EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S4	24	(ZD4054 or ZD-4054 or ZD "4054" or Zibotentan) and (ZD "1839" or ZD-1839 or ZD1839 or Iressa or Gefitinib)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 07:46
S5	2724	(endothelin or ET-1 or ET1 or ET S1 or ETAR) and (epidermal growth factor or epidermal-growth factor or EGF or EGFR)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 07:48
S6	1068	(endothelin or ET-1 or ET1 or ET S1 or ETAR) same (epidermal growth factor or epidermal-growth factor or EGF or EGFR)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 07:48
S7	580	(endothelin or ET-1 or ET1 or ET S1 or ETAR) with (epidermal growth factor or epidermal-growth factor or EGF or EGFR)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 08:11
S8	1	((endothelin or ET-1 or ET1 or ET S1 or ETAR) and (epidermal growth factor or epidermal-growth factor or EGF or EGFR)).ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 07:52
S9	21	((endothelin or ET-1 or ET1 or ET S1 or ETAR) and (epidermal growth factor or epidermal-growth factor or EGF or EGFR)).ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 07:59
S10	21	S9 and endothelin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 07:59

EAST Search History

S11	137	(endothelin or ET-1 or ET1 or ET S1 or ETAR) with (epidermal growth factor or epidermal-growth factor or EGF or EGFR) and lung cancer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 08:12
S12	0	(endothelin or ET-1 or ET1 or ET S1 or ETAR) with (epidermal growth factor or epidermal-growth factor or EGF or EGFR) with lung cancer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 08:12
S13	18	(ZD4054 or ZD "4054" or ZD-4054 or zibotetan) and lung cancer	US-PGPUB; USPAT	ADJ	ON	2007/09/06 09:44
S16	28	ZD4054 or ZD "4054" or ZD-4054 or zibotetan	US-PGPUB; USPAT	ADJ	ON	2007/09/06 09:46
S17	28	ZD4054 or ZD "4054" or ZD-4054 or zibotetan	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2007/09/06 10:19

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NEWS 4	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
NEWS 5	MAY 21	BIOSIS reloaded and enhanced with archival data
NEWS 6	MAY 21	TOXCENTER enhanced with BIOSIS reload
NEWS 7	MAY 21	CA/CAplus enhanced with additional kind codes for German patents
NEWS 8	MAY 22	CA/CAplus enhanced with IPC reclassification in Japanese patents
NEWS 9	JUN 27	CA/CAplus enhanced with pre-1967 CAS Registry Numbers
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NEWS 13	JUL 02	LMEDLINE coverage updated
NEWS 14	JUL 02	SCISEARCH enhanced with complete author names
NEWS 15	JUL 02	CHEMCATS accession numbers revised
NEWS 16	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 17	JUL 16	CAplus enhanced with French and German abstracts
NEWS 18	JUL 18	CA/CAplus patent coverage enhanced
NEWS 19	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 20	JUL 30	USGENE now available on STN
NEWS 21	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 22	AUG 06	BEILSTEIN updated with new compounds
NEWS 23	AUG 06	FSTA enhanced with new thesaurus edition
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NEWS 25	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
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NEWS 27	AUG 27	USPATOLD now available on STN
NEWS 28	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data

NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,
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=> File caplus medline

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FULL ESTIMATED COST	1.26	1.26

FILE 'CAPLUS' ENTERED AT 08:22:28 ON 06 SEP 2007
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=> s nature/rwk (s) 379/rvl (s) 1996/rpy (s) 557/rpg
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'RVL' IS NOT A VALID FIELD CODE
'RPY' IS NOT A VALID FIELD CODE
'RPG' IS NOT A VALID FIELD CODE
L1 709 NATURE/RWK (S) 379/RVL (S) 1996/RPY (S) 557/RPG

=> L1 and lung cancer
L1 IS NOT A RECOGNIZED COMMAND
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"HELP COMMANDS" at an arrow prompt (=>).

=> s L1 and lung cancer
L2 4 L1 AND LUNG CANCER

=> d L2 1-4 ibib abs

L2 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1004765 CAPLUS
DOCUMENT NUMBER: 142:212673
TITLE: Characterization of the B2 receptor and activity of bradykinin analogs in SHP-77 cell line by Cytosensor microphysiometer
AUTHOR(S): Bironaite, Daiva; Gera, Lajos; Stewart, John M.
CORPORATE SOURCE: Department of Developmental Biology, Institute of Biochemistry, Vilnius, 2600, Lithuania
SOURCE: Chemico-Biological Interactions (2004), 150(3), 283-293
CODEN: CBINA8; ISSN: 0009-2797
PUBLISHER: Elsevier Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Cytosensor microphysiometer device (Mol. Devices, Sunnyvale, CA) is capable of measuring the rate at which cells acidify their environment in response to ligand-receptor binding. By measuring the extracellular acidification response (ECAR) we characterized some aspects of ligand-B2 receptor interaction in SHP-77 cell line. SHP-77 cells maximally acidified their environment within 30 s after the exposure to bradykinin (BK) or the BK agonist, B9972, with the maximum effect seen at a ligands concentration of 1 μM. Fetal bovine serum (FBS) modulated the binding of BK or B9972, showing that B9972 is a partial agonist. In addition, the binding of BK agonist or antagonist to the B2 receptor showed different ECAR and different interaction with other intracellular and plasma membrane proteins. Our microphysiometrical results showed that two parameters, antagonist binding affinity (pD2) and antagonist potency (pIC50) are

required to characterize BK antagonist activity for the B2 receptor in the SHP-77 cell line. The previously used parameter of B2 antagonist activity, pA2, had high variation and poor correlation with the inhibition of SHP-77 cell growth in vitro and suppression of tumor growth when SHP-77 cells were injected to mice. Our results permit us to conclude that BK agonists and antagonists differ in their interactions with the B2 receptor and consequently elicit different cell responses. Based on our results, we have developed a new microphysiometrical assay for analyzing the activity of BK agonists and antagonist in SHP-77 cells, which may facilitate the discovery of new potent anticancer drugs.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:72655 CAPLUS
DOCUMENT NUMBER: 140:138588
TITLE: Smart drugs in prostate cancer
AUTHOR(S): Van der Poel, H. G.
CORPORATE SOURCE: Department Urology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, 1066 CX, Neth.
SOURCE: European Urology (2004), 45(1), 1-17
CODEN: EUURAV; ISSN: 0302-2838
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Objectives: Growth signaling is instrumental in tumor development. Insight into signaling pathways by mol. and cellular biol. has changed the development of new anticancer agents. Outside the field of urol. specifically targeted drugs such as imatinib mesylate and gefitinib showed impressive anticancer activity in chronic myeloid leukemia and non-small cell lung cancer, resp. Methods: Literature search of PubMed documented publications and abstrs. from meetings. Results: Preclin. data in prostate cancer shows upregulation of a wide variety of growth factors and their receptors such as PDGF, EGF, IGF, FGF, and VEGF suggesting efficacy of agents targeting these pathways. Here the preclin. evidence and first clin. data on the use of growth signal targeting in prostate cancer is reviewed. Although some anticancer efficacy of signal transduction inhibition monotherapy was reported, combination with chemotherapy and radiotherapy seemed most promising in prostate cancer. Conclusion: So-called smart drugs are small mols. targeted at specific growth signaling pathways. These new drugs will dominate clin. trials in the years to come either as single-drug modality, but more likely as combination treatment.
REFERENCE COUNT: 178 THERE ARE 178 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:26469 CAPLUS
DOCUMENT NUMBER: 140:70147
TITLE: The epidermal growth factor receptor pathway and its inhibition as anticancer therapy
AUTHOR(S): Janmaat, M. L.; Giaccone, G.
CORPORATE SOURCE: Department of Medical Oncology, Vrije Universiteit Medical Center, Amsterdam, Neth.
SOURCE: Drugs of Today (2003), 39(Suppl. C, New Approaches in Cancer Research), 61-80
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Epidermal growth factor receptor (EGFR) is commonly overexpressed in a number of epithelial malignancies and is often associated with an aggressive phenotype [e.g., non-small cell lung

cancer (NSCLC) and bladder cancer]. EGFR is present in over 50% of cases of NSCLC, head and neck squamous cell carcinomas (HNSCC) and colon cancer. Several EGFR-targeting agents have been recently developed (C225, ABX-EGF, E7.6.3, EMD 55900, ICR62, ZD1839, CP358774, PD168393, CGP75166/PKI166, CGP59326A, BIBX1382). The two most advanced EGFR inhibitors in development are C225 and ZD1839. C225 is an antibody directed against the ligand-binding domain of human EGFR, which competes for receptor binding with EGF and other ligands. In vitro, C225 inhibits EGFR tyrosine kinase activity and proliferation of EGFR-overexpressing squamous cell carcinoma cell lines. Synergy was observed with doxorubicin, cisplatin and radiation in preclin. models. In phase I trials, major toxicity has been dermatol. (rash and acneic skin reactions); allergic reactions have also been observed in about 3% of cases. This agent, administered i.v. once weekly, is presently in phase III trials in HNSCC and colon cancer. ZD1839, a synthetic mol. which targets the EGFR ATP binding site, is a very specific inhibitor of EGFR tyrosine kinase activity. Synergy has been observed with paclitaxel and cisplatin. In phase I trials, responses were seen in advanced NSCLC, and cutaneous toxicity and diarrhea were the most important side effects. Oral chronic daily administration is feasible. Two large randomized trials have been completed in advanced NSCLC in combination with chemotherapy. A large phase II study in second and third line has demonstrated a single agent activity of 18.5%. Another large phase II study in patients who received prior platinum and docetaxel obtained a response rate of 11%. There was no difference in response rate between the 250 and the 500 mg/day doses, but side effects were higher in patients who received the 500 mg dose. A very similar small mol., OSI-774, has also shown activity in this setting. Two large randomized phase III studies of ZD1839 have recently been completed and analyzed in which two doses of ZD1839 (250 or 500 mg/day) or placebo were given in combination with two different chemotherapy regimens (carboplatin-paclitaxel or carboplatin-gemcitabine). These studies failed to demonstrate an increase in survival by adding ZD1839 together with chemotherapy in patients with advanced NSCLC.

REFERENCE COUNT: 128 THERE ARE 128 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:396348 CAPLUS

DOCUMENT NUMBER: 135:102620

TITLE: The role of small bioactive peptides and cell surface peptidases in androgen independent prostate cancer

AUTHOR(S): Nelson, Joel B.

CORPORATE SOURCE: Brady Urol. Inst., Johns Hopkins Med. Inst., Baltimore, MD, USA

SOURCE: Prostate Cancer (2001), 433-447. Editor(s): Chung, Leland W. K.; Isaacs, William B.; Simons, Jonathan W. Humana Press Inc.: Totowa, N. J. CODEN: 69BIZN

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

AB A review with 120 refs. At current rates of diagnosis, a man in the United States has a one-in-five chance that invasive prostate cancer will develop in his lifetime. This rate is nearly twice that of lung cancer and three times that of colorectal cancer. Death from prostate cancer is the second leading cause of death from cancer in men in the United States. Almost every man with advanced prostate cancer will undergo androgen ablation therapy and in time, most will progress. The central characteristic of fatal prostate cancer is androgen independence. These facts were established in 1941, when therapeutic castration was first described, and, unfortunately, still hold true as the 1990s drew to a close. Historically, there has been an inverse relationship between efforts to maximize the efficacy of hormonal therapy for prostate cancer and the outcomes of those efforts: thousands of patients studied and billions of dollars spent repeatedly show hormonal therapy to have

dramatic-yet ultimately ineffective-therapeutic effects. Although a number of growth and survival factors have been implicated in the androgen independent phenotype of prostate cancer, there has been no translation of these findings to effective therapy. This review is not confined to the classic neuroendocrine phenotype (which, in its small cell or carcinoid manifestations represents a fraction of prostate cancers)-it examines a recent series of related observations about the role of the small bioactive peptides bombesin, endothelin-1 (ET-1), and neurotensin in prostate cancer. These peptides-which have compelling biol. effects in prostate cancer-act through specific, high-affinity heptahelical, G-protein-coupled receptors. Collectively, recent observations may provide a broader understanding of androgen independent prostate cancer. Excitement for targeting these pathways in therapy has been fueled by early clin. trial results: the use of an endothelin-receptor antagonist has resulted in both objective and subjective responses.
REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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'2003' NOT A VALID FIELD CODE
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L3 411 L1 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> s ((endothelin or et1 or et 1 or et-1 or etar) and (egf or egfr or epidermal growth factor))/ab
L4 476 ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR OR EPIDERMAL GROWTH FACTOR))/AB

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L5 12 L3 AND L4

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L6 71 ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR OR EPIDERMAL GROWTH FACTOR))/TI

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L7 5 L3 AND L6

=> S L5 and L7
L8 5 L5 AND L7

=> D L8 1-5 ibib abs

L8 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:981107 CAPLUS
DOCUMENT NUMBER: 138:232159
TITLE: Characterization of Ca2+ channels involved in ET-1-induced transactivation of EGF receptors
AUTHOR(S): Kawanabe, Yoshifumi; Hashimoto, Nobuo; Masaki, Tomoh
CORPORATE SOURCE: Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, 606-8501, Japan
SOURCE: American Journal of Physiology (2002), 283(6, Pt. 2), H2671-H2675
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to demonstrate the involvement of Ca2+ influx through voltage-independent Ca2+ channels (VICCs) in endothelin-1 (ET-1)-induced transactivation of epidermal growth factor receptor protein

tyrosine kinase (EGFR PTK) using the Ca2+ channel blockers LOE-908 and SKF-96365 in rabbit internal carotid artery vascular smooth muscle cells. ET-1-induced EGFR PTK transactivation was completely inhibited by AG-1478, which is a specific inhibitor of EGFR PTK. In the absence of extracellular Ca2+, the magnitude of EGFR PTK transactivation was near the basal level. Based on sensitivity to nifedipine, which is a specific blocker of voltage-operated Ca2+ channels (VOCCs), VOCCs have minor roles in EGFR PTK transactivation. In contrast, Ca2+ influx through voltage-independent Ca2+ channels (VICCs) plays an important role in EGFR PTK transactivation. Moreover, based on the sensitivity of VICCs to SKF-96365 and LOE-908, VICCs were shown to consist of two types of Ca2+-permeable nonselective cation channels (NSCCs), which are designated NSCC-1 and NSCC-2, and a store-operated Ca2+ channel. In summary, Ca2+ influx through VICCs plays an essential role in ET -1-induced EGFR PTK transactivation in rabbit internal carotid artery vascular smooth muscle cells.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:126156 CAPLUS

DOCUMENT NUMBER: 136:364144

TITLE: Role of EGF Receptor and Pyk2 in Endothelin-1-induced ERK Activation in Rat Cardiomyocytes

AUTHOR(S): Kodama, Hiroaki; Fukuda, Keiichi; Takahashi, Toshiyuki; Sano, Motoaki; Kato, Takahiro; Tahara, Satoko; Hakuno, Daihiko; Sato, Toshihiko; Manabe, Tomohiro; Konishi, Fusako; Ogawa, Satoshi

CORPORATE SOURCE: Cardiopulmonary Division, Department of Internal Medicine, Keio University School of Medicine, Shinjuku, Tokyo, 160-8582, Japan

SOURCE: Journal of Molecular and Cellular Cardiology (2002), 34(2), 139-150
CODEN: JMCDAY; ISSN: 0022-2828

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB G protein-coupled receptor (GPCR)-evoked signal transduction pathways leading to the activation of extracellular signal-regulated kinases (ERK) are quite different among cell types. In cardiomyocytes, much attention has been focused on the activation of protein kinase C (PKC) or mobilization of intracellular Ca2+ ([Ca2+]i), however, the contributions of tyrosine kinases are controversial. In the present study, the authors characterized the signaling pathways involving tyrosine kinases, Pyk2 and epidermal growth factor receptor (EGFR), and their contribution to ERK activation in cultured cardiomyocytes. The authors initially investigated the potential involvement of [Ca2+]i and PKC on the activation of these kinases in endothelin -stimulated cardiomyocytes. Interestingly, activation of Pyk2 was abrogated by chelating [Ca2+]i or by downregulation of PKC, whereas transactivation of EGFR was solely dependent on PKC. By using a compound that selectively interferes with EGFR (AG1478), c-Src (PP1), or disrupts actin cytoskeleton (cytochalasin D), the authors demonstrated that cytochalasin D completely inhibited the activation of Pyk2, but not that of EGFR, whereas AG1478 did not inhibit the activation of Pyk2, indicating that transactivation of EGFR and signaling pathways involving Pyk2 were distinct pathways. Furthermore, activation of ERK and Shc, and c- fos gene expression were significantly inhibited by AG1478, but not by cytochalasin D or PP1. Overexpression of deletion mutant of EGFR attenuated the activation of ERK. These facts demonstrated the existence of two distinct tyrosine kinase pathways requiring Pyk2 or EGFR downstream from GPCR in cardiomyocytes. EGFR was Ca2+-independently activated and predominantly

contributed to Shc/ERK/c-fos activation, while Pyk2 or c-Src contributed less to it. (c) 2002 Academic Press.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:615916 CAPLUS
DOCUMENT NUMBER: 131:318224
TITLE: Endothelin-mediated vascular growth requires p42/p44 mitogen-activated protein kinase and p70 S6 kinase cascades via transactivation of epidermal growth factor receptor
AUTHOR(S): Iwasaki, Hiroaki; Eguchi, Satoru; Ueno, Hikaru; Marumo, Fumiaki; Hirata, Yukio
CORPORATE SOURCE: Division of Endocrinology and Metabolism, the Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo, 113-8519, Japan
SOURCE: Endocrinology (1999), 140(10), 4659-4668
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Endothelin-1 (ET-1), a potent endothelium-derived vasoconstrictor peptide, exerts a growth-promoting effect on vascular smooth muscle cells, implicating its pathogenic role in vascular remodeling. To gain insight into the cellular and mol. mechanism whereby ET-1 induces vascular growth, the authors studied whether transactivation of receptor tyrosine kinases, such as epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor, are required for activation of p42/p44 mitogen-activated protein (MAP) kinase and p70 S6 kinase (p70S6K), and subsequent growth-promotion by ET-1 in cultured rat vascular smooth muscle cells. Immunoblotting with antiphosphotyrosine antibody revealed that ET-1 rapidly (within 2 min) and transiently induced tyrosine phosphorylation of several proteins, among which 180-kDa protein was shown to be EGFR . ET-1 rapidly increased association of EGFR and Shc with glutathione-S-transferase-Grb2 fusion protein. The ET-1-induced activation of MAP kinase was reduced by an EGFR kinase inhibitor (AG1478) but not by a platelet-derived growth factor receptor kinase inhibitor (AG1296). AG1478 dose-dependently decreased ET-1-stimulated MAP kinase activity as well as [3H]leucine and [3H]thymidine uptake. The ET-1 -induced tyrosine phosphorylation of EGFR, as well as MAP kinase activation, was inhibited by an ETA receptor antagonist and intracellular Ca2+ antagonists but not by an ETB receptor antagonist, pertussis toxin, or protein kinase C inhibitors. In addition, dominant neg. mutant of H-Ras and a MAP kinase kinase (MEK-1) inhibitor (PD98059) completely blocked ET-1-induced MAP kinase activation as well as [3H]leucine and [3H]thymidine uptake. Both AG1478 and PD98059 inhibited ET-1-induced phosphorylation and activation of p70S6K. Furthermore, rapamycin, a selective inhibitor of mammalian target of rapamycin, completely blocked ET-1-stimulated [3H]leucine and [3H]thymidine uptake. These results suggest that ETA receptor-mediated vascular growth by ET-1 requires both MAP kinase and p70S6K cascades mediated partly via Ca2+-dependent EGFR transactivation.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:312801 CAPLUS
DOCUMENT NUMBER: 129:50062
TITLE: Endothelin-1 stimulates DNA synthesis of

vascular smooth-muscle cells through transactivation of epidermal growth factor receptor

AUTHOR(S): Iwasaki, Hiroaki; Eguchi, Satoru; Marumo, Fumiaki; Hirata, Yukio

CORPORATE SOURCE: Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo, 113, Japan

SOURCE: Journal of Cardiovascular Pharmacology (1998), 31(Suppl. 1, Endothelin V), S182-S184
CODEN: JCPCDT; ISSN: 0160-2446

PUBLISHER: Lippincott-Raven Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To elucidate the mol. mechanism of the mitogenic effect of endothelin-1 (ET-1) on vascular smooth muscle cells (VSMCs), we studied the effect of AG1478, a novel epidermal growth factor receptor (EGFR) kinase inhibitor, on p42/44 mitogen-activated protein (MAP) kinase activation, c-Fos expression, and DNA synthesis stimulated by ET-1. AG1478 dose-dependently (2.5+10-8 M-2.5+10-7 M) inhibited ET-1-induced MAP kinase activation. The ET-1-induced c-Fos protein expression was inhibited by AG1478 (2.5+10-7 M). AG1478 also dose-dependently inhibited ET-1-stimulated [3H]thymidine incorporation. These data suggest that ET-1 induces MAP kinase activation, c-Fos expression, and promotes proliferation of VSMCs via transactivation of EGFR.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:354923 CAPLUS

DOCUMENT NUMBER: 127:61168

TITLE: ET-1 cooperates with EGF to induce mitogenesis via a PTX-sensitive pathway in airway smooth muscle cells

AUTHOR(S): Fujitani, Yasushi; Bertrand, Claude

CORPORATE SOURCE: Dep. Respiratory Diseases and Allergy, Ciba-Geigy Ltd., Basel, CH-4002, Switz.

SOURCE: American Journal of Physiology (1997), 272(5, Pt. 1), C1492-C1498
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have examined the mitogenic effect of endothelin-1 (ET-1) alone or in combination with EGF in cultured airway smooth muscle cells (ASM) from guinea pig. ET-1 showed a weak mitogenic activity compared with the effect of EGF. However, when ET-1 and EGF were applied simultaneously, ET-1 synergistically enhanced the mitogenic activity of EGF. Neither inhibition of phospholipase C-β nor depletion of protein kinase C affected this synergism. Pertussis toxin (PTX), a Gi protein inhibitor, abolished the synergistic effect of ET-1 on EGF-induced mitogenesis. ET-1 induced a transient mitogen-activated protein (MAP) kinase activation peaking at 5 min. In contrast, EGF induced a stronger signal that was maintained for <20 min. However, concomitant stimulation of ASM with ET-1 and EGF caused an enhanced MAP kinase activation compared with EGF alone. Moreover, PTX abolished the enhanced MAP kinase activation observed in this condition. These results indicate that ET-1 can interact with an EGF-induced mitogenic axis through the Gi protein-dependent pathway, which is distinct from its direct mitogenic pathway.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2            4 S L1 AND LUNG CANCER
L3          411 S L1 AND (PY<2003 OR AY<2003 OR PRY<2003)
L4          476 S ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR
L5           12 S L3 AND L4
L6           71 S ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR
L7            5 S L3 AND L6
L8            5 S L5 AND L7

=> S L4 and lung cancer
L9            0 L4 AND LUNG CANCER

=> S L6 and lung cancer
L10           0 L6 AND LUNG CANCER

=> s L4 and cancer
L11          45 L4 AND CANCER

=> s L6 and cancer
L12           8 L6 AND CANCER

=> D l12 1-8 ibib abs

L12  ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2007:748964  CAPLUS
TITLE:                    Combined targeting of endothelin A receptor
                          and epidermal growth
                          factor receptor in ovarian cancer
                          shows enhanced antitumor activity
AUTHOR(S):                Rosano, Laura; Di Castro, Valeriana; Spinella,
                          Francesca; Tortora, Giampaolo; Nicotra, Maria Rita;
                          Natali, Pier Giorgio; Bagnato, Anna
CORPORATE SOURCE:         Molecular Pathology and Immunology Laboratories,
                          Regina Elena Cancer Institute, Institute of Molecular
                          Biology and Pathology, National Research Council,
                          Rome, Endocrinology and Molecular Oncology Department,
                          University of Naples, Federico II, Naples, Italy
SOURCE:                   Cancer Research (2007), 67(13), 6351-6359
                          CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER:                American Association for Cancer Research
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Ovarian carcinomas overexpress endothelin A receptors (ETAR) and epidermal
     growth factor (EGF) receptor (EGFR). In these cells, endothelin-1 (ET-1)
     triggers mitogenic and invasive signaling pathways that are in part
     mediated by EGFR transactivation. Combined targeting of ETAR, by the
     specific ETAR antagonist ZD4054, and of EGFR by the EGFR inhibitor
     gefitinib (IRESSA), may offer improvements in ovarian carcinoma treatment.
     In HEY and OVCA 433 ovarian carcinoma cells, ET-1 or EGF induced rapid
     activation of EGFR, p42/44 mitogen-activated protein kinase (MAPK), and
     AKT. ZD4054 was able to reduce the ET-1-induced EGFR transactivation.
     Gefitinib significantly inhibited EGF- and ET-1-induced EGFR
     phosphorylation, but incompletely reduced the ET-1-induced activation of
     downstream targets. ZD4054 plus gefitinib resulted in a greater
     inhibition of EGFR, MAPK, and AKT phosphorylation, indicating the critical
     role of these interconnected signaling proteins. ZD4054 effectively
     inhibited cell proliferation, invasiveness, and vascular endothelial
```

growth factor (VEGF) secretion. Concomitantly, ZD4054 enhanced apoptosis and E-cadherin promoter activity and expression. In both cell lines, the drug combination resulted in a significant decrease in cell proliferation (65%), invasion (52%), and VEGF production (50%), accompanied by a 2-fold increase in apoptosis. The coadministration of ZD4054 enhanced the efficacy of gefitinib leading to partial (82%) or complete tumor regression on HEY ovarian carcinoma xenografts. Antitumor effects were paralleled by biochem. and immunohistol. evidence of decreased vascularization, Ki-67, matrix metalloproteinase-2 (MMP-2), VEGF, MAPK and EGFR, and enhanced E-cadherin expression. The cross-signaling between the EGFR/ETAR pathways provides a rationale to combine EGFR inhibitors with ETAR antagonists, identifying new effective therapeutic opportunities for ovarian cancer.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:38448 CAPLUS
DOCUMENT NUMBER: 142:152954
TITLE: Endothelin-1 stimulates cyclooxygenase-2 expression in ovarian cancer cells through multiple signaling pathways: Evidence for involvement of transactivation of the epidermal growth factor receptor
AUTHOR(S): Spinella, Francesca; Rosano, Laura; Elia, Giacomo; Di Castro, Valeriana; Natali, Pier Giorgio; Bagnato, Anna
CORPORATE SOURCE: Laboratories of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, Italy
SOURCE: Journal of Cardiovascular Pharmacology (2004), 44(Suppl. 1), S140-S143
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ovarian carcinoma cells release high amts. of endothelin-1 and exhibit increased expression of endothelin-A receptor. Engagement of the endothelin-A receptor triggers tumor growth, survival, neoangiogenesis and invasion. Cyclooxygenase-1 and cyclooxygenase-2 are enzymes involved in the production of prostaglandins and play a role in the regulation of tumor progression in several malignancies, including ovarian carcinomas. Endothelin-1 significantly increases the expression of cyclooxygenase-1 and cyclooxygenase-2 mRNA and protein, the activity of the cyclooxygenase-2 promoter, and the release of prostaglandin E2 from two ovarian carcinoma cell lines, HEY and OVCA 433. The cyclooxygenase-2 inhibitor, NS-398 drastically decreased the endothelin-1-induced prostaglandin E2 production and vascular endothelial growth factor upregulation, indicating a role for cyclooxygenase-2 in endothelin-1-induced vascular endothelial growth factor-mediated angiogenesis. In this study the authors demonstrated that endothelin-1-induced cyclooxygenase-2 and related prostaglandin E2 release were dependent upon the activation of endothelin-A receptor and of multiple mitogen-activated protein kinase signal pathways, including extracellular signal-regulated kinase 1/2 kinase, p38 mitogen-activated protein kinase and the transactivation of the epidermal growth factor receptor. In human ovarian xenografts, the levels of cyclooxygenase-2 protein expression were significantly reduced following treatment with the endothelin-A receptor selective antagonist, atrasentan, compared with untreated mice. These results suggest that the pharmacol. blocking of endothelin-A receptor is an attractive strategy to control the cyclooxygenase-2 protein expression in ovarian carcinoma.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:354796 CAPLUS
DOCUMENT NUMBER: 140:368653
TITLE: Endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for the treatment of cancer
INVENTOR(S): Boyle, Francis Thomas; Curwen, Jon Owen; Gallagher, Neil James; Hancox, Ursula Joy; Hughes, Andrew Mark; Johnstone, Donna; Taylor, Sian Tomiko; Tonge, David William
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035057	A1	20040429	WO 2003-GB4347	20031007
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2501959	A1	20040429	CA 2003-2501959	20031007
AU 2003269259	A1	20040504	AU 2003-269259	20031007
AU 2003269259	B2	20070315		
EP 1553950	A1	20050720	EP 2003-751038	20031007
EP 1553950	B1	20070808		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003015140	A	20050816	BR 2003-15140	20031007
CN 1703224	A	20051130	CN 2003-80101310	20031007
JP 2006510605	T	20060330	JP 2004-544431	20031007
AT 369136	T	20070815	AT 2003-751038	20031007
NO 2005001658	A	20050506	NO 2005-1658	20050404
MX 2005PA03808	A	20050608	MX 2005-PA3808	20050408
ZA 2005002874	A	20060222	ZA 2005-2874	20050408
US 2006122180	A1	20060608	US 2005-530794	20050408
PRIORITY APPLN. INFO.:			GB 2002-23854 A	20021012
			WO 2003-GB4347 W	20031007

AB A combination, comprising an endothelin receptor antagonist (e.g. ZD4054), or a pharmaceutically acceptable salt thereof, and an EGF receptor tyrosine kinase inhibitor (e.g. ZD1839), or a pharmaceutically acceptable salt thereof, is described. The combination of the invention is useful for the treatment of cancer, e.g. prostate cancer.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:702602 CAPLUS
DOCUMENT NUMBER: 134:3338
TITLE: Transactivation of the epidermal growth factor receptor in endothelin-1-induced mitogenic signaling in human ovarian carcinoma cells
AUTHOR(S): Vacca, Fabrizio; Bagnato, Anna; Catt, Kevin J.; Tecce, Raffaele
CORPORATE SOURCE: Laboratory of Molecular Pathology and Ultrastructure,

Regina Elena Cancer Institute, Rome, 00158, Italy
SOURCE: Cancer Research (2000), 60(18), 5310-5317
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Endothelin (ET)-1 is produced in ovarian carcinoma cells and is known to act through ETA receptors as an autocrine growth factor in vitro and in vivo. In OVCA 433 human ovarian carcinoma cells, ET-1 caused phosphorylation of the epidermal growth factor receptor (EGF-R) that was accompanied by phosphorylation of Shc and its recruitment complexed with Grb2. These findings suggested that an EGF-R/ras-dependent pathway may contribute to the activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) 2 and mitogenic signaling induced by ET-1 in these cells. Specific inhibition of EGF-R kinase activity by tyrphostin AG1478 prevented ET-1-induced transactivation of the EGF-R, as well as Shc phosphorylation and recruitment with Grb2. Furthermore, ET-1-induced activation of Erk 2 was partially inhibited by tyrphostin AG1478. In accord with this finding, the mitogenic action of ET-1 in OVCA 433 cells was also significantly reduced by a concentration of tyrphostin AG1478 that abolished the growth response of EGF-stimulated cells. Inhibition of protein kinase C activity, which contributes to the proliferative action of ET-1 in OVCA 433 cells, had no effect on the activation of Erk 2 by ET-1, which suggests that this effect of protein kinase C does not involve ras-independent activation of Erk 2. Inhibition by wortmannin of PI3-kinase activity, which has been implicated in ET-1 and other G protein-coupled receptor (GPCR)-mediated signaling pathways, reduced Erk 2 activation by ET-1 but had no effect on ET-1-induced EGF-R and Shc phosphorylation. These findings indicate that ET-1-induced stimulation of Erk 2 phosphorylation, and mitogenic responses in OVCA 433 ovarian cancer cells are mediated in part by signaling pathways that are initiated by transactivation of the EGF-R.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:421261 CAPLUS
DOCUMENT NUMBER: 129:198380
TITLE: The Ets-1 and Ets-2 transcription factors activate the promoters for invasion-associated urokinase and collagenase genes in response to epidermal growth factor
AUTHOR(S): Watabe, Tetsuya; Yoshidai, Koichi; Shindoh, Masanobu; Kaya, Mitsunori; Fujikawa, Keiko; Sato, Hiroshi; Seiki, Motoharu; Ishi, Seiichi; Fujinaga, Kei
CORPORATE SOURCE: Department of Molecular Biology, Cancer Research Institute, Sapporo Medical University, School of Medicine, Sapporo, 060, Japan
SOURCE: International Journal of Cancer (1998), 77(1), 128-137
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Urokinase plasminogen activator (uPA) has been associated with invasion and metastasis in breast cancer. The expression of uPA and 92 kDa type IV collagenase (gelatinase BIMMP-9) is regulated by growth factors, receptor-type tyrosine kinases and cytoplasmic oncoproteins. Here, the authors have identified transcriptional requirements for the induction of uPA and 92 kDa type IV collagenase by epidermal growth factor (EGF). EGF stimulates the motile and invasive activities specifically in the ErbB-2-overexpressing SK-BR-3 cells. Expression of extracellular matrix-degrading proteases including type I collagenase/MMP-1, 92 kDa type IV collagenase/ MMP-9, uPA and uPA receptor were induced. EGF also transiently stimulated expression of the transcription factors Ets-1 and

Ets-2. Reporter transfection assays revealed the activation of uPA and MMP-9 collagenase promoters by EGF and the requirement of each of the composite Ets and AP-1 transcription factor binding sites for an EGF response. Most notably, transfections with the Ets-1 and Ets-2 expression vectors potentiated uPA and MMP-9 promoter activation in response to EGF. Mutation of the threonine 75 residue of chicken Ets-2 conserved in the Pointed group of the Ets family proteins abrogated the ability of Ets-2 to collaborate with EGF. Ets-1 and Ets-2 were highly expressed in invasive breast tumor cell lines. The authors' results suggest that Ets-1 and Ets-2 provide the link connecting EGF stimuli with activation of uPA and 92 kDa type IV collagenase promoters and may contribute to invasion phenotypes.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2007404203 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17616694
TITLE: Combined targeting of endothelin A receptor and epidermal growth factor receptor in ovarian cancer shows enhanced antitumor activity.
AUTHOR: Rosano Laura; Di Castro Valeriana; Spinella Francesca; Tortora Giampaolo; Nicotra Maria Rita; Natali Pier Giorgio; Bagnato Anna
CORPORATE SOURCE: Molecular Pathology Laboratory, Regina Elena Cancer Institute, Rome, Italy.
SOURCE: Cancer research, (2007 Jul 1) Vol. 67, No. 13, pp. 6351-9. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200707
ENTRY DATE: Entered STN: 12 Jul 2007
Last Updated on STN: 28 Jul 2007
Entered Medline: 27 Jul 2007

AB Ovarian carcinomas overexpress endothelin A receptors (ET(A)R) and epidermal growth factor (EGF) receptor (EGFR). In these cells, endothelin-1 (ET-1) triggers mitogenic and invasive signaling pathways that are in part mediated by EGFR transactivation. Combined targeting of ET(A)R, by the specific ET(A)R antagonist ZD4054, and of EGFR by the EGFR inhibitor gefitinib (IRESSA), may offer improvements in ovarian carcinoma treatment. In HEY and OVCA 433 ovarian carcinoma cells, ET-1 or EGF induced rapid activation of EGFR, p42/44 mitogen-activated protein kinase (MAPK), and AKT. ZD4054 was able to reduce the ET-1-induced EGFR transactivation. Gefitinib significantly inhibited EGF- and ET-1-induced EGFR phosphorylation, but incompletely reduced the ET-1-induced activation of downstream targets. ZD4054 plus gefitinib resulted in a greater inhibition of EGFR, MAPK, and AKT phosphorylation, indicating the critical role of these interconnected signaling proteins. ZD4054 effectively inhibited cell proliferation, invasiveness, and vascular endothelial growth factor (VEGF) secretion. Concomitantly, ZD4054 enhanced apoptosis and E-cadherin promoter activity and expression. In both cell lines, the drug combination resulted in a significant decrease in cell proliferation (65%), invasion (52%), and VEGF production (50%), accompanied by a 2-fold increase in apoptosis. The coadministration of ZD4054 enhanced the efficacy of gefitinib leading to partial (82%) or complete tumor regression on HEY ovarian carcinoma xenografts. Antitumor effects were paralleled by biochemical and immunohistologic evidence of decreased vascularization, Ki-67, matrix metalloproteinase-2 (MMP-2), VEGF, MAPK and EGFR, and enhanced E-cadherin expression. The cross-signaling between the EGFR/ET(A)R pathways provides a rationale to combine EGFR inhibitors with ET(A)R antagonists, identifying new effective therapeutic opportunities

for ovarian cancer.

L12 ANSWER 7 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2000463833 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11016663
TITLE: Transactivation of the epidermal growth factor receptor in endothelin-1-induced mitogenic signaling in human ovarian carcinoma cells.
AUTHOR: Vacca F; Bagnato A; Catt K J; Tecce R
CORPORATE SOURCE: Laboratory of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, Italy.
SOURCE: Cancer research, (2000 Sep 15) Vol. 60, No. 18, pp. 5310-7. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 27 Oct 2000
Last Updated on STN: 27 Oct 2000
Entered Medline: 13 Oct 2000

AB Endothelin (ET)-1 is produced in ovarian carcinoma cells and is known to act through ET(A) receptors as an autocrine growth factor in vitro and in vivo. In OVCA 433 human ovarian carcinoma cells, ET-1 caused phosphorylation of the epidermal growth factor receptor (EGF-R) that was accompanied by phosphorylation of Shc and its recruitment complexed with Grb2. These findings suggested that an EGF-R/ras-dependent pathway may contribute to the activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) 2 and mitogenic signaling induced by ET-1 in these cells. Specific inhibition of EGF-R kinase activity by tyrphostin AG1478 prevented ET-1-induced transactivation of the EGF-R, as well as Shc phosphorylation and recruitment with Grb2. Furthermore, ET-1-induced activation of Erk 2 was partially inhibited by tyrphostin AG1478. In accord with this finding, the mitogenic action of ET-1 in OVCA 433 cells was also significantly reduced by a concentration of tyrphostin AG1478 that abolished the growth response of EGF-stimulated cells. Inhibition of protein kinase C activity, which contributes to the proliferative action of ET-1 in OVCA 433 cells, had no effect on the activation of Erk 2 by ET-1, which suggests that this effect of protein kinase C does not involve ras-independent activation of Erk 2. Inhibition by wortmannin of PI3-kinase activity, which has been implicated in ET-1 and other G protein-coupled receptor (GPCR)-mediated signaling pathways, reduced Erk 2 activation by ET-1 but had no effect on ET-1-induced EGF-R and Shc phosphorylation. These findings indicate that ET-1-induced stimulation of Erk 2 phosphorylation, and mitogenic responses in OVCA 433 ovarian cancer cells are mediated in part by signaling pathways that are initiated by transactivation of the EGF-R.

L12 ANSWER 8 OF 8 MEDLINE on STN
ACCESSION NUMBER: 1998301275 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9639404
TITLE: The Ets-1 and Ets-2 transcription factors activate the promoters for invasion-associated urokinase and collagenase genes in response to epidermal growth factor.
AUTHOR: Watabe T; Yoshida K; Shindoh M; Kaya M; Fujikawa K; Sato H; Seiki M; Ishii S; Fujinaga K
CORPORATE SOURCE: Department of Molecular Biology, Cancer Research Institute, Sapporo Medical University, School of Medicine, Japan.
SOURCE: International journal of cancer. Journal international du cancer, (1998 Jul 3) Vol. 77, No. 1, pp. 128-37. Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 16 Jul 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 7 Jul 1998

AB Urokinase plasminogen activator (uPA) has been associated with invasion and metastasis in breast cancer. The expression of uPA and 92 kDa type IV collagenase (gelatinase B/MMP-9) is regulated by growth factors, receptor-type tyrosine kinases and cytoplasmic oncoproteins. Here, we have identified transcriptional requirements for the induction of uPA and 92 kDa type IV collagenase by epidermal growth factor (EGF). EGF stimulates the motile and invasive activities specifically in the ErbB-2-overexpressing SK-BR-3 cells. Expression of extracellular matrix-degrading proteases including type I collagenase/MMP-1, 92 kDa type IV collagenase/MMP-9, uPA and uPA receptor were induced. EGF also transiently stimulated expression of the transcription factors Ets-1 and Ets-2. Reporter transfection assays revealed the activation of uPA and MMP-9 collagenase promoters by EGF and the requirement of each of the composite Ets and AP-1 transcription factor binding sites for an EGF response. Most notably, transfections with the Ets-1 and Ets-2 expression vectors potentiated uPA and MMP-9 promoter activation in response to EGF. Mutation of the threonine 75 residue of chicken Ets-2 conserved in the Pointed group of the Ets family proteins abrogated the ability of Ets-2 to collaborate with EGF. Ets-1 and Ets-2 were highly expressed in invasive breast tumor cell lines. Our results suggest that Ets-1 and Ets-2 provide the link connecting EGF stimuli with activation of uPA and 92 kDa type IV collagenase promoters and may contribute to invasion phenotypes.

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(FILE 'HOME' ENTERED AT 08:18:45 ON 06 SEP 2007)

FILE 'CAPLUS, MEDLINE' ENTERED AT 08:22:28 ON 06 SEP 2007
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L3 411 S L1 AND (PY<2003 OR AY<2003 OR PRY<2003)
L4 476 S ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR
L5 12 S L3 AND L4
L6 71 S ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR
L7 5 S L3 AND L6
L8 5 S L5 AND L7
L9 0 S L4 AND LUNG CANCER
L10 0 S L6 AND LUNG CANCER
L11 45 S L4 AND CANCER
L12 8 S L6 AND CANCER

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L13 71 L4 AND L6

=> S L13 and cancer
L14 8 L13 AND CANCER

=> D l14 1-8 ibib abs

L14 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:748964 CAPLUS
TITLE: Combined targeting of endothelin A receptor and epidermal growth factor receptor in ovarian cancer shows enhanced antitumor activity
AUTHOR(S): Rosano, Laura; Di Castro, Valeriana; Spinella,

Francesca; Tortora, Giampaolo; Nicotra, Maria Rita; Natali, Pier Giorgio; Bagnato, Anna

CORPORATE SOURCE: Molecular Pathology and Immunology Laboratories, Regina Elena Cancer Institute, Institute of Molecular Biology and Pathology, National Research Council, Rome, Endocrinology and Molecular Oncology Department, University of Naples, Federico II, Naples, Italy

SOURCE: Cancer Research (2007), 67(13), 6351-6359
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Ovarian carcinomas overexpress endothelin A receptors (ETAR) and epidermal growth factor (EGF) receptor (EGFR). In these cells, endothelin-1 (ET-1) triggers mitogenic and invasive signaling pathways that are in part mediated by EGFR transactivation. Combined targeting of ETAR, by the specific ETAR antagonist ZD4054, and of EGFR by the EGFR inhibitor gefitinib (IRESSA), may offer improvements in ovarian carcinoma treatment. In HEY and OVCA 433 ovarian carcinoma cells, ET-1 or EGF induced rapid activation of EGFR, p42/44 mitogen-activated protein kinase (MAPK), and AKT. ZD4054 was able to reduce the ET-1-induced EGFR transactivation. Gefitinib significantly inhibited EGF- and ET-1-induced EGFR phosphorylation, but incompletely reduced the ET-1-induced activation of downstream targets. ZD4054 plus gefitinib resulted in a greater inhibition of EGFR, MAPK, and AKT phosphorylation, indicating the critical role of these interconnected signaling proteins. ZD4054 effectively inhibited cell proliferation, invasiveness, and vascular endothelial growth factor (VEGF) secretion. Concomitantly, ZD4054 enhanced apoptosis and E-cadherin promoter activity and expression. In both cell lines, the drug combination resulted in a significant decrease in cell proliferation (65%), invasion (52%), and VEGF production (50%), accompanied by a 2-fold increase in apoptosis. The coadministration of ZD4054 enhanced the efficacy of gefitinib leading to partial (82%) or complete tumor regression on HEY ovarian carcinoma xenografts. Antitumor effects were paralleled by biochem. and immunohistol. evidence of decreased vascularization, Ki-67, matrix metalloproteinase-2 (MMP-2), VEGF, MAPK and EGFR, and enhanced E-cadherin expression. The cross-signaling between the EGFR/ETAR pathways provides a rationale to combine EGFR inhibitors with ETAR antagonists, identifying new effective therapeutic opportunities for ovarian cancer.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:38448 CAPLUS

DOCUMENT NUMBER: 142:152954

TITLE: Endothelin-1 stimulates cyclooxygenase-2 expression in ovarian cancer cells through multiple signaling pathways: Evidence for involvement of transactivation of the epidermal growth factor receptor

AUTHOR(S): Spinella, Francesca; Rosano, Laura; Elia, Giacomo; Di Castro, Valeriana; Natali, Pier Giorgio; Bagnato, Anna

CORPORATE SOURCE: Laboratories of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, Italy

SOURCE: Journal of Cardiovascular Pharmacology (2004), 44(Suppl. 1), S140-S143
CODEN: JCPCDT; ISSN: 0160-2446

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ovarian carcinoma cells release high amts. of endothelin-1 and exhibit increased expression of endothelin-A receptor. Engagement of the endothelin-A receptor triggers tumor growth, survival, neoangiogenesis and invasion. Cyclooxygenase-1 and cyclooxygenase-2 are enzymes involved in the production of prostaglandins and play a role in the regulation of tumor progression in several malignancies, including ovarian carcinomas. Endothelin-1 significantly increases the expression of cyclooxygenase-1 and cyclooxygenase-2 mRNA and protein, the activity of the cyclooxygenase-2 promoter, and the release of prostaglandin E2 from two ovarian carcinoma cell lines, HEY and OVCA 433. The cyclooxygenase-2 inhibitor, NS-398 drastically decreased the endothelin-1-induced prostaglandin E2 production and vascular endothelial growth factor upregulation, indicating a role for cyclooxygenase-2 in endothelin-1-induced vascular endothelial growth factor-mediated angiogenesis. In this study the authors demonstrated that endothelin-1-induced cyclooxygenase-2 and related prostaglandin E2 release were dependent upon the activation of endothelin-A receptor and of multiple mitogen-activated protein kinase signal pathways, including extracellular signal-regulated kinase 1/2 kinase, p38 mitogen-activated protein kinase and the transactivation of the epidermal growth factor receptor. In human ovarian xenografts, the levels of cyclooxygenase-2 protein expression were significantly reduced following treatment with the endothelin-A receptor selective antagonist, atrasentan, compared with untreated mice. These results suggest that the pharmacol. blocking of endothelin-A receptor is an attractive strategy to control the cyclooxygenase-2 protein expression in ovarian carcinoma.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:354796 CAPLUS
DOCUMENT NUMBER: 140:368653
TITLE: Endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for the treatment of cancer
INVENTOR(S): Boyle, Francis Thomas; Curwen, Jon Owen; Gallagher, Neil James; Hancox, Ursula Joy; Hughes, Andrew Mark; Johnstone, Donna; Taylor, Sian Tomiko; Tonge, David William
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035057	A1	20040429	WO 2003-GB4347	20031007
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2501959	A1	20040429	CA 2003-2501959	20031007
AU 2003269259	A1	20040504	AU 2003-269259	20031007

AU 2003269259	B2	20070315			
EP 1553950	A1	20050720	EP 2003-751038		20031007
EP 1553950	B1	20070808			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003015140	A	20050816	BR 2003-15140		20031007
CN 1703224	A	20051130	CN 2003-80101310		20031007
JP 2006510605	T	20060330	JP 2004-544431		20031007
AT 369136	T	20070815	AT 2003-751038		20031007
NO 2005001658	A	20050506	NO 2005-1658		20050404
MX 2005PA03808	A	20050608	MX 2005-PA3808		20050408
ZA 2005002874	A	20060222	ZA 2005-2874		20050408
US 2006122180	A1	20060608	US 2005-530794		20050408
PRIORITY APPLN. INFO.:			GB 2002-23854	A	20021012
			WO 2003-GB4347	W	20031007

AB A combination, comprising an endothelin receptor antagonist (e.g. ZD4054), or a pharmaceutically acceptable salt thereof, and an EGF receptor tyrosine kinase inhibitor (e.g. ZD1839), or a pharmaceutically acceptable salt thereof, is described. The combination of the invention is useful for the treatment of cancer, e.g. prostate cancer.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:702602 CAPLUS

DOCUMENT NUMBER: 134:3338

TITLE: Transactivation of the epidermal growth factor receptor in endothelin-1-induced mitogenic signaling in human ovarian carcinoma cells

AUTHOR(S): Vacca, Fabrizio; Bagnato, Anna; Catt, Kevin J.; Tecce, Raffaele

CORPORATE SOURCE: Laboratory of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, 00158, Italy

SOURCE: Cancer Research (2000), 60(18), 5310-5317
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Endothelin (ET)-1 is produced in ovarian carcinoma cells and is known to act through ETA receptors as an autocrine growth factor in vitro and in vivo. In OVCA 433 human ovarian carcinoma cells, ET-1 caused phosphorylation of the epidermal growth factor receptor (EGF -R) that was accompanied by phosphorylation of Shc and its recruitment complexed with Grb2. These findings suggested that an EGF -R/ras-dependent pathway may contribute to the activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) 2 and mitogenic signaling induced by ET-1 in these cells. Specific inhibition of EGF-R kinase activity by tyrphostin AG1478 prevented ET-1-induced transactivation of the EGF-R, as well as Shc phosphorylation and recruitment with Grb2. Furthermore, ET-1-induced activation of Erk 2 was partially inhibited by tyrphostin AG1478. In accord with this finding, the mitogenic action of ET-1 in OVCA 433 cells was also significantly reduced by a concentration of tyrphostin AG1478 that abolished the growth response of EGF-stimulated cells. Inhibition of protein kinase C activity, which contributes to the proliferative action of ET-1 in OVCA 433 cells, had no effect on the activation of Erk 2 by ET-1, which suggests that this effect of protein kinase C does not involve ras-independent activation of Erk 2. Inhibition by wortmannin of PI3-kinase activity, which has been implicated in ET-1

and other G protein-coupled receptor (GPCR)-mediated signaling pathways, reduced Erk 2 activation by ET-1 but had no effect on ET-1-induced EGF-R and Shc phosphorylation. These findings indicate that ET-1-induced stimulation of Erk 2 phosphorylation, and mitogenic responses in OVCA 433 ovarian cancer cells are mediated in part by signaling pathways that are initiated by transactivation of the EGF-R.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:421261 CAPLUS
DOCUMENT NUMBER: 129:198380
TITLE: The Ets-1 and Ets-2 transcription factors activate the promoters for invasion-associated urokinase and collagenase genes in response to epidermal growth factor
AUTHOR(S): Watabe, Tetsuya; Yoshidai, Koichi; Shindoh, Masanobu; Kaya, Mitsunori; Fujikawa, Keiko; Sato, Hiroshi; Seiki, Motoharu; Ishi, Seiichi; Fujinaga, Kei
CORPORATE SOURCE: Department of Molecular Biology, Cancer Research Institute, Sapporo Medical University, School of Medicine, Sapporo, 060, Japan
SOURCE: International Journal of Cancer (1998), 77(1), 128-137 CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Urokinase plasminogen activator (uPA) has been associated with invasion and metastasis in breast cancer. The expression of uPA and 92 kDa type IV collagenase (gelatinase BIMMP-9) is regulated by growth factors, receptor-type tyrosine kinases and cytoplasmic oncoproteins. Here, the authors have identified transcriptional requirements for the induction of uPA and 92 kDa type IV collagenase by epidermal growth factor (EGF). EGF stimulates the motile and invasive activities specifically in the ErbB-2-overexpressing SK-BR-3 cells. Expression of extracellular matrix-degrading proteases including type I collagenase/MMP-1, 92 kDa type IV collagenase/ MMP-9, uPA and uPA receptor were induced. EGF also transiently stimulated expression of the transcription factors Ets-1 and Ets-2. Reporter transfection assays revealed the activation of uPA and MMP-9 collagenase promoters by EGF and the requirement of each of the composite Ets and AP-1 transcription factor binding sites for an EGF response. Most notably, transfections with the Ets-1 and Ets-2 expression vectors potentiated uPA and MMP-9 promoter activation in response to EGF. Mutation of the threonine 75 residue of chicken Ets-2 conserved in the Pointed group of the Ets family proteins abrogated the ability of Ets-2 to collaborate with EGF. Ets-1 and Ets-2 were highly expressed in invasive breast tumor cell lines. The authors' results suggest that Ets-1 and Ets-2 provide the link connecting EGF stimuli with activation of uPA and 92 kDa type IV collagenase promoters and may contribute to invasion phenotypes.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2007404203 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17616694
TITLE: Combined targeting of endothelin A receptor and epidermal growth factor receptor in ovarian cancer shows enhanced antitumor activity.
AUTHOR: Rosano Laura; Di Castro Valeriana; Spinella Francesca; Tortora Giampaolo; Nicotra Maria Rita; Natali Pier Giorgio;

Bagnato Anna
CORPORATE SOURCE: Molecular Pathology Laboratory, Regina Elena Cancer Institute, Rome, Italy.
SOURCE: Cancer research, (2007 Jul 1) Vol. 67, No. 13, pp. 6351-9. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200707
ENTRY DATE: Entered STN: 12 Jul 2007
Last Updated on STN: 28 Jul 2007
Entered Medline: 27 Jul 2007

AB Ovarian carcinomas overexpress endothelin A receptors (ET(A)R) and epidermal growth factor (EGF) receptor (EGFR). In these cells, endothelin-1 (ET-1) triggers mitogenic and invasive signaling pathways that are in part mediated by EGFR transactivation. Combined targeting of ET(A)R, by the specific ET(A)R antagonist ZD4054, and of EGFR by the EGFR inhibitor gefitinib (IRESSA), may offer improvements in ovarian carcinoma treatment. In HEY and OVCA 433 ovarian carcinoma cells, ET-1 or EGF induced rapid activation of EGFR, p42/44 mitogen-activated protein kinase (MAPK), and AKT. ZD4054 was able to reduce the ET-1 -induced EGFR transactivation. Gefitinib significantly inhibited EGF- and ET-1-induced EGFR phosphorylation, but incompletely reduced the ET-1 -induced activation of downstream targets. ZD4054 plus gefitinib resulted in a greater inhibition of EGFR, MAPK, and AKT phosphorylation, indicating the critical role of these interconnected signaling proteins. ZD4054 effectively inhibited cell proliferation, invasiveness, and vascular endothelial growth factor (VEGF) secretion. Concomitantly, ZD4054 enhanced apoptosis and E-cadherin promoter activity and expression. In both cell lines, the drug combination resulted in a significant decrease in cell proliferation (65%), invasion (52%), and VEGF production (50%), accompanied by a 2-fold increase in apoptosis. The coadministration of ZD4054 enhanced the efficacy of gefitinib leading to partial (82%) or complete tumor regression on HEY ovarian carcinoma xenografts. Antitumor effects were paralleled by biochemical and immunohistologic evidence of decreased vascularization, Ki-67, matrix metalloproteinase-2 (MMP-2), VEGF, MAPK and EGFR, and enhanced E-cadherin expression. The cross-signaling between the EGFR /ET(A)R pathways provides a rationale to combine EGFR inhibitors with ET(A)R antagonists, identifying new effective therapeutic opportunities for ovarian cancer.

L14 ANSWER 7 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2000463833 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11016663
TITLE: Transactivation of the epidermal growth factor receptor in endothelin-1-induced mitogenic signaling in human ovarian carcinoma cells.
AUTHOR: Vacca F; Bagnato A; Catt K J; Tecce R
CORPORATE SOURCE: Laboratory of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, Italy.
SOURCE: Cancer research, (2000 Sep 15) Vol. 60, No. 18, pp. 5310-7. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 27 Oct 2000

Last Updated on STN: 27 Oct 2000
Entered Medline: 13 Oct 2000

AB Endothelin (ET)-1 is produced in ovarian carcinoma cells and is known to act through ET(A) receptors as an autocrine growth factor in vitro and in vivo. In OVCA 433 human ovarian carcinoma cells, ET-1 caused phosphorylation of the epidermal growth factor receptor (EGF -R) that was accompanied by phosphorylation of Shc and its recruitment complexed with Grb2. These findings suggested that an EGF -R/ras-dependent pathway may contribute to the activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) 2 and mitogenic signaling induced by ET-1 in these cells. Specific inhibition of EGF-R kinase activity by tyrphostin AG1478 prevented ET-1-induced transactivation of the EGF-R, as well as Shc phosphorylation and recruitment with Grb2. Furthermore, ET-1-induced activation of Erk 2 was partially inhibited by tyrphostin AG1478. In accord with this finding, the mitogenic action of ET-1 in OVCA 433 cells was also significantly reduced by a concentration of tyrphostin AG1478 that abolished the growth response of EGF -stimulated cells. Inhibition of protein kinase C activity, which contributes to the proliferative action of ET-1 in OVCA 433 cells, had no effect on the activation of Erk 2 by ET-1, which suggests that this effect of protein kinase C does not involve ras-independent activation of Erk 2. Inhibition by wortmannin of PI3-kinase activity, which has been implicated in ET-1 and other G protein-coupled receptor (GPCR)-mediated signaling pathways, reduced Erk 2 activation by ET-1 but had no effect on ET-1-induced EGF-R and Shc phosphorylation. These findings indicate that ET-1-induced stimulation of Erk 2 phosphorylation, and mitogenic responses in OVCA 433 ovarian cancer cells are mediated in part by signaling pathways that are initiated by transactivation of the EGF-R.

L14 ANSWER 8 OF 8 MEDLINE on STN
ACCESSION NUMBER: 1998301275 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9639404
TITLE: The Ets-1 and Ets-2 transcription factors activate the promoters for invasion-associated urokinase and collagenase genes in response to epidermal growth factor.
AUTHOR: Watabe T; Yoshida K; Shindoh M; Kaya M; Fujikawa K; Sato H; Seiki M; Ishii S; Fujinaga K
CORPORATE SOURCE: Department of Molecular Biology, Cancer Research Institute, Sapporo Medical University, School of Medicine, Japan.
SOURCE: International journal of cancer. Journal international du cancer, (1998 Jul 3) Vol. 77, No. 1, pp. 128-37. Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 16 Jul 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 7 Jul 1998

AB Urokinase plasminogen activator (uPA) has been associated with invasion and metastasis in breast cancer. The expression of uPA and 92 kDa type IV collagenase (gelatinase B/MMP-9) is regulated by growth factors, receptor-type tyrosine kinases and cytoplasmic oncoproteins. Here, we have identified transcriptional requirements for the induction of uPA and 92 kDa type IV collagenase by epidermal growth factor (EGF). EGF stimulates the motile and invasive activities specifically in the ErbB-2-overexpressing SK-BR-3

cells. Expression of extracellular matrix-degrading proteases including type I collagenase/MMP-1, 92 kDa type IV collagenase/MMP-9, uPA and uPA receptor were induced. EGF also transiently stimulated expression of the transcription factors Ets-1 and Ets-2. Reporter transfection assays revealed the activation of uPA and MMP-9 collagenase promoters by EGF and the requirement of each of the composite Ets and AP-1 transcription factor binding sites for an EGF response. Most notably, transfections with the Ets-1 and Ets-2 expression vectors potentiated uPA and MMP-9 promoter activation in response to EGF. Mutation of the threonine 75 residue of chicken Ets-2 conserved in the Pointed group of the Ets family proteins abrogated the ability of Ets-2 to collaborate with EGF. Ets-1 and Ets-2 were highly expressed in invasive breast tumor cell lines. Our results suggest that Ets-1 and Ets-2 provide the link connecting EGF stimuli with activation of uPA and 92 kDa type IV collagenase promoters and may contribute to invasion phenotypes.

=> D his

(FILE 'HOME' ENTERED AT 08:18:45 ON 06 SEP 2007)

FILE 'CAPLUS, MEDLINE' ENTERED AT 08:22:28 ON 06 SEP 2007
L1 709 S NATURE/RWK (S) 379/RVL (S) 1996/RPY (S) 557/RPG
L2 4 S L1 AND LUNG CANCER
L3 411 S L1 AND (PY<2003 OR AY<2003 OR PRY<2003)
L4 476 S ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR
L5 12 S L3 AND L4
L6 71 S ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR
L7 5 S L3 AND L6
L8 5 S L5 AND L7
L9 0 S L4 AND LUNG CANCER
L10 0 S L6 AND LUNG CANCER
L11 45 S L4 AND CANCER
L12 8 S L6 AND CANCER
L13 71 S L4 AND L6
L14 8 S L13 AND CANCER

=> S l3 and cancer
L15 33 L3 AND CANCER

=> s L3 and lung cancer
L16 1 L3 AND LUNG CANCER

=> d L16 ibib abs

L16 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:396348 CAPLUS
DOCUMENT NUMBER: 135:102620
TITLE: The role of small bioactive peptides and cell surface peptidases in androgen independent prostate cancer
AUTHOR(S): Nelson, Joel B.
CORPORATE SOURCE: Brady Urol. Inst., Johns Hopkins Med. Inst., Baltimore, MD, USA
SOURCE: Prostate Cancer (2001), 433-447. Editor(s): Chung, Leland W. K.; Isaacs, William B.; Simons, Jonathan W. Humana Press Inc.: Totowa, N. J. CODEN: 69BIZN
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 120 refs. At current rates of diagnosis, a man in the United States has a one-in-five chance that invasive prostate cancer will develop in his lifetime. This rate is nearly twice that of lung cancer and three times that of colorectal cancer. Death from

prostate cancer is the second leading cause of death from cancer in men in the United States. Almost every man with advanced prostate cancer will undergo androgen ablation therapy and in time, most will progress. The central characteristic of fatal prostate cancer is androgen independence. These facts were established in 1941, when therapeutic castration was first described, and, unfortunately, still hold true as the 1990s drew to a close. Historically, there has been an inverse relationship between efforts to maximize the efficacy of hormonal therapy for prostate cancer and the outcomes of those efforts: thousands of patients studied and billions of dollars spent repeatedly show hormonal therapy to have dramatic-yet ultimately ineffective-therapeutic effects. Although a number of growth and survival factors have been implicated in the androgen independent phenotype of prostate cancer, there has been no translation of these findings to effective therapy. This review is not confined to the classic neuroendocrine phenotype (which, in its small cell or carcinoid manifestations represents a fraction of prostate cancers)-it examines a recent series of related observations about the role of the small bioactive peptides bombesin, endothelin-1 (ET-1), and neurotensin in prostate cancer. These peptides-which have compelling biol. effects in prostate cancer-act through specific, high-affinity heptahelical, G-protein-coupled receptors. Collectively, recent observations may provide a broader understanding of androgen independent prostate cancer. Excitement for targeting these pathways in therapy has been fueled by early clin. trial results: the use of an endothelin-receptor antagonist has resulted in both objective and subjective responses.

REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s ((endothelin or et1 or et 1 or et-1 or etar) (S) (egf or egfr or epidermal growth factor)) (S) cancer
L17 22 ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) (S) (EGF OR EGFR OR EPIDERMAL GROWTH FACTOR)) (S) CANCER

=> D l17 22 ibib abs

L17 ANSWER 22 OF 22 MEDLINE on STN
ACCESSION NUMBER: 91065733 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2249889
TITLE: Mitogenic peptides in breast cyst fluid: relationship with intracystic electrolyte ratios.
AUTHOR: Lai L C; Ghatei M A; Takahashi K; Patel K V; Schrey M P; Ghilchik M W; Bloom S R; James V H
CORPORATE SOURCE: Department of Chemical Pathology, St. Mary's Hospital Medical School, Imperial College of Science, Technology and Medicine, London, UK.
SOURCE: International journal of cancer. Journal international du cancer, (1990 Dec 15) Vol. 46, No. 6, pp. 1014-6. Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 8 Mar 1991
Last Updated on STN: 3 Mar 2000
Entered Medline: 16 Jan 1991

AB Women with palpable breast cysts which are lined with apocrine epithelium may be at higher risk of developing breast cancer than women with breast cysts which are lined with flattened epithelium, the former group being characterized by intracystic sodium to potassium ratios below 3, while the latter group has intracystic sodium to potassium ratios above 3. In this study the distribution of intracystic concentrations of the mitogenic peptides, epidermal growth factor,

endothelin and gastrin-releasing peptide in the 2 groups of breast cysts were compared to see whether differences in concentrations between the 2 cyst groups might provide an explanation for the higher risk of breast cancer observed in women with "apocrine" breast cysts. The concentrations of epidermal growth factor and gastrin-releasing peptide were significantly higher in the low electrolyte ratio group (p less than 0.001). There was no difference in endothelin concentrations between the 2 groups. Negative correlations were found between epidermal growth factor concentrations and Na+/K+ and between gastrin-releasing peptide concentrations and Na+/K+ (p less than 0.001). A positive correlation was found between gastrin-releasing peptide and epidermal growth factor concentrations in breast cyst fluid (p less than 0.001). The significantly higher intracystic concentrations of both epidermal growth factor and gastrin-releasing peptide in the low-electrolyte-ratio group may provide an explanation for the higher risk of breast cancer which has been observed in women with "apocrine" breast cysts.

=> D l17 21 ibib abs

L17 ANSWER 21 OF 22 MEDLINE on STN
ACCESSION NUMBER: 96223664 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8630991
TITLE: Endothelin-1 production and decreased endothelin B receptor expression in advanced prostate cancer.
AUTHOR: Nelson J B; Chan-Tack K; Hedican S P; Magnuson S R; Opgenorth T J; Bova G S; Simons J W
CORPORATE SOURCE: James Buchanan Brady Urological Institute Research Laboratories, Johns Hopkins Hospital, Baltimore, Maryland 21287-2411, USA.
CONTRACT NUMBER: CA-58236 (NCI)
SOURCE: Cancer research, (1996 Feb 15) Vol. 56, No. 4, pp. 663-8. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 15 Jul 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 3 Jul 1996

AB The potent vasoconstrictor endothelin-1 (ET-1) is at its highest concentration in the normal human ejaculate and is associated with the progression of metastatic prostate cancer. ET-1 protein expression is detected in situ in 14 of 14 primary cancers and 14 of 16 metastatic sites of human prostatic carcinoma. Exogenous ET-1 induces prostate cancer proliferation directly and enhances the mitogenic effects of insulin-like growth factor I, insulin-like growth factor II, platelet-derived growth factor, basic fibroblast growth factor, and epidermal growth factor in serum-free conditions in vitro. The ETA-selective receptor antagonist A-127722 inhibits ET-1-stimulated growth, but the ETB-selective receptor antagonist BQ-788 does not. ET-3, an ETB-selective agonist, also had no effect on prostate cancer growth. No specific ETB-binding sites could be demonstrated in any established human prostate cancer cell line tested, and ETB mRNA, detected by reverse transcription PCR, was reduced. The predominance of ETB binding on human benign prostatic epithelial tissue is not present in metastatic prostate cancer by autoradiography. In human prostate cancer progression to metastases, ET-1 and ETA expression are retained, whereas ETB receptor expression is reduced.

=> d l17 20 ibib abs

L17 ANSWER 20 OF 22 MEDLINE on STN
ACCESSION NUMBER: 97238707 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9102218
TITLE: Activation of mitogenic signaling by endothelin 1 in ovarian carcinoma cells.
AUTHOR: Bagnato A; Tecce R; Di Castro V; Catt K J
CORPORATE SOURCE: Laboratory of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, Italy.
SOURCE: Cancer research, (1997 Apr 1) Vol. 57, No. 7, pp. 1306-11. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 24 Apr 1997
Last Updated on STN: 19 Dec 2002
Entered Medline: 17 Apr 1997

AB Endothelin 1 (ET-1) is produced in ovarian cancer cell lines and has been shown to act through ET(A) receptors as an autocrine growth factor to promote tumor cell proliferation in vitro. In OVCA 433 cells, the efficacy of ET-1 as a stimulus of [3H]thymidine incorporation was equivalent to that of epidermal growth factor. ET-1 also stimulated the rapid expression of c-fos, an action mediated by ET(A) receptors. The mitogenic action of ET-1 was not mediated by a pertussis toxin-sensitive G protein. An analysis of the effects of inhibition and depletion of protein kinase C (PKC) on mitogenic responses demonstrated that PKC was necessary but not sufficient for maximal stimulation by ET-1. In quiescent OVCA 433 cells, ET-1-induced stimulation of [3H]thymidine incorporation was prevented by two structurally distinct inhibitors of tyrosine kinase, herbimycin A and genistein. These results indicate that both PKC and protein tyrosine kinase participate in ET-1-stimulated mitogenic signaling. ET-1 rapidly stimulated tyrosine phosphorylation of several cellular proteins, among which p125FAK and p42 mitogen-activated protein kinase were identified. The additivity between the potent mitogenic actions of ET-1 and epidermal growth factor is consistent with the independence of their signal transduction pathways in ovarian cancer cells. These findings also indicate that intracellular signaling between the ET(A) receptor and a yet unidentified tyrosine kinase is involved in the mitogenic response to ET-1.

=> D l17 19 ibib abs

L17 ANSWER 19 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2000463833 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11016663
TITLE: Transactivation of the epidermal growth factor receptor in endothelin-1-induced mitogenic signaling in human ovarian carcinoma cells.
AUTHOR: Vacca F; Bagnato A; Catt K J; Tecce R
CORPORATE SOURCE: Laboratory of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, Italy.
SOURCE: Cancer research, (2000 Sep 15) Vol. 60, No. 18, pp. 5310-7. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010

ENTRY DATE: Entered STN: 27 Oct 2000
Last Updated on STN: 27 Oct 2000
Entered Medline: 13 Oct 2000

AB Endothelin (ET)-1 is produced in ovarian carcinoma cells and is known to act through ET(A) receptors as an autocrine growth factor in vitro and in vivo. In OVCA 433 human ovarian carcinoma cells, ET-1 caused phosphorylation of the epidermal growth factor receptor (EGF-R) that was accompanied by phosphorylation of Shc and its recruitment complexed with Grb2. These findings suggested that an EGF-R/ras-dependent pathway may contribute to the activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) 2 and mitogenic signaling induced by ET-1 in these cells. Specific inhibition of EGF-R kinase activity by tyrphostin AG1478 prevented ET-1-induced transactivation of the EGF-R, as well as Shc phosphorylation and recruitment with Grb2. Furthermore, ET-1-induced activation of Erk 2 was partially inhibited by tyrphostin AG1478. In accord with this finding, the mitogenic action of ET-1 in OVCA 433 cells was also significantly reduced by a concentration of tyrphostin AG1478 that abolished the growth response of EGF-stimulated cells. Inhibition of protein kinase C activity, which contributes to the proliferative action of ET-1 in OVCA 433 cells, had no effect on the activation of Erk 2 by ET-1, which suggests that this effect of protein kinase C does not involve ras-independent activation of Erk 2. Inhibition by wortmannin of PI3-kinase activity, which has been implicated in ET-1 and other G protein-coupled receptor (GPCR)-mediated signaling pathways, reduced Erk 2 activation by ET-1 but had no effect on ET-1-induced EGF-R and Shc phosphorylation. These findings indicate that ET-1 -induced stimulation of Erk 2 phosphorylation, and mitogenic responses in OVCA 433 ovarian cancer cells are mediated in part by signaling pathways that are initiated by transactivation of the EGF-R.

=> DE l17 18 ibib abs
DE IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d l17 18 ibib abs

L17 ANSWER 18 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2001697440 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11746273
TITLE: Endothelin-1 production by prostate cancer cell lines is up-regulated by factors involved in cancer progression and down-regulated by androgens.
AUTHOR: Granchi S; Brocchi S; Bonaccorsi L; Baldi E; Vinci M C; Forti G; Serio M; Maggi M
CORPORATE SOURCE: Department of Clinical Physiopathology, Unit of Andrology, University of Florence, Florence, Italy.
SOURCE: The Prostate, (2001 Dec 1) Vol. 49, No. 4, pp. 267-77. Journal code: 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 18 Dec 2001
Last Updated on STN: 25 Jan 2002
Entered Medline: 8 Jan 2002

AB BACKGROUND: Recent data demonstrate that endothelin-1 (ET-1) concentration increases in plasma of men with advanced, hormone-refractory prostate adenocarcinoma. In addition, ET-1 is involved in osteblastic remodelling and new bone formation, suggesting a role for this vasoactive peptide in

the metastatic progression of prostate cancer to the bone. METHODS: We investigated the regulation of ET-1 expression in androgen-sensitive and insensitive prostate cancer cell lines by androgens and several factors involved in progression of prostate cancer (EGF) and bone remodelling (TGFbeta-1, IL1-alpha and IGF-1). RESULTS: Northern analysis and radio immunoassay demonstrated that all the ET-1 pathways are tuned off in the androgen-sensitive LNCaP cell line when compared to the androgen-insensitive PC-3 and DU145. In PC-3 cells transfected with a full-length androgen receptor expression vector (PC-3-AR), treatment with androgens reduced gene expression and secretion of ET-1 without affecting the gene expression of ET-3. Collectively, these data support a role for androgens in the regulation of ET-1 production by prostate adenocarcinoma cells. In PC-3 and DU145 cells, ET-1 gene expression and secretion were up-regulated by TGFbeta-1, EGF and IL1-alpha, whereas IGF-1 was ineffective. Conversely, none of the treatments affected ECE-1 or ET-3 gene expression. CONCLUSIONS: In conclusion, ET-1 production by prostate adenocarcinoma cells is down-regulated by androgens and up-regulated by factors involved in tumour progression indicating a role for this peptide in the biology of prostate cancer. In view of the role exerted by ET-1 in the process of bone metastasis, our data suggest the use of ET-1 receptor antagonists in the treatment of advanced prostate cancer.

=> D l17 17 ibib abs

L17 ANSWER 17 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2005630590 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16167350
TITLE: Transactivating agonists of the EGF receptor require Tyr 845 phosphorylation for induction of DNA synthesis.
AUTHOR: Boerner Julie L; Biscardi Jacqueline S; Silva Corinne M; Parsons Sarah J
CORPORATE SOURCE: Department of Microbiology, The Cancer Center, University of Virginia Health System, Charlottesville, Virginia 22908, USA.
CONTRACT NUMBER: CA93028 (NCI)
R01 CA71449 (NCI)
R01 CA85462 (NCI)
SOURCE: Molecular carcinogenesis, (2005 Dec) Vol. 44, No. 4, pp. 262-73.
Journal code: 8811105. ISSN: 0899-1987.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200601
ENTRY DATE: Entered STN: 29 Nov 2005
Last Updated on STN: 6 Jan 2006
Entered Medline: 5 Jan 2006

AB Signaling networks play important roles in cancer progression. For example, overexpression of the epidermal growth factor receptor (EGFR) is a poor prognostic indicator in multiple tumor types. Recent studies have postulated that the EGFR functions as a central conduit for signaling by different classes of cell surface receptors. In this study, we demonstrated that c-Src-dependent phosphorylation of tyrosine 845 (Tyr 845) on EGFR was required for DNA synthesis induced by the G protein-coupled agonists, endothelin (ET) and lysophosphatidic acid (LPA), and the cytokine, growth hormone (GH), in murine fibroblast and breast cancer model systems. In addition, we showed that a dominant interfering form of signal transducer and activator of

transcription (STAT)5b (a downstream effector of phospho-Tyr 845 [pY845] in fibroblasts) abrogates DNA synthesis induced by all agonists in the breast cancer model. To further characterize the role of Tyr 845, a pY845-containing peptide was microinjected into SKBr3 breast cancer cells and murine fibroblasts, and was found to ablate EGF-stimulated S-phase entry in both cell systems. Taken together, these findings suggested that pY845 is critical for DNA synthesis induced by a variety of mitogens and that its signaling effectors may include but are not limited to STAT5b.

=> d l17 16 ibib abs

L17 ANSWER 16 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2006426324 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16848363
TITLE: Molecular-targeted therapy for hormone-refractory prostate cancer.
AUTHOR: Nishimura Kazuo; Takayama Hitoshi; Nakayama Masashi; Nonomura Norio; Okuyama Akihiko
CORPORATE SOURCE: The Department of Urology, Graduate School of Medicine, Osaka University.
SOURCE: Hinyokika kiyo. Acta urologica Japonica, (2006 Jun) Vol. 52, No. 6, pp. 487-90.
Journal code: 0421145. ISSN: 0018-1994.
PUB. COUNTRY: Japan
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200607
ENTRY DATE: Entered STN: 20 Jul 2006
Last Updated on STN: 26 Jul 2006
Entered Medline: 25 Jul 2006
AB Molecular-targeted therapy is to treat pathologic pathways specifically in tumor cell or tumor microenvironment. Specific molecular-targeted therapeutic agents for hormone-refractory prostate cancer (HRPC) include endothelin-A receptor antagonist, EGF receptor (EGFR) inhibitor, platelet derived growth factor receptor (PDGFR) inhibitor, nuclear factor of kappaB (NF-kappaB) inhibitor, cyclooxygenase-2 (COX2) inhibitor, and active form of Vitamin D. These agents have been investigated in clinical trials. So far, none of the above-mentioned agent has shown a sufficient clinical efficacy alone. However, docetaxel-based combinations with thalidomide or calcitriol have promising clinical activities. Further investigations are needed to optimize the molecular-targeted agents in the combinations with chemotherapeutic agents for the treatment of HRPC.

=> d l17 15 ibib abs

L17 ANSWER 15 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2006560071 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 16986005
TITLE: Emerging pharmacologic therapies for prostate cancer.
AUTHOR: Trachtenberg J
SOURCE: Reviews in urology, (2001) Vol. 3 Suppl 3, pp. S23-8.
Journal code: 100889067. ISSN: 1523-6161.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED
ENTRY DATE: Entered STN: 21 Sep 2006
Last Updated on STN: 12 Dec 2006
AB The last decade has seen explosive growth in the therapy of prostate cancer. Three areas of therapeutics are emerging: 1) new compounds with

novel uses; 2) available compounds with new applications; and 3) new compounds applied to established indications. The novel compounds target specific receptor sites of cancer pathways and attack cancer cells with less effect on normal tissue. Earlyphase trials with compounds targeting the endothelin-A and EGF receptors have shown encouraging results in hormone-refractory prostate cancer. In addition, the Early Prostate Cancer Trial of over 8000 men is currently underway to determine the benefit of adjuvant androgen ablation with bicalutamide in men with localized prostate cancer. Early results show a significant 42% reduction in the progression of the disease in the bicalutamide treatment arm. Further, in large, phase 3 clinical trials in patients needing androgen ablation, the GnRH antagonist abarelix caused no testosterone surge and demonstrated a significantly more rapid decline in serum testosterone to the castrate level than did an LHRH agonist analogue. Abarelix should thus have application as a monotherapy in patients who need a rapid onset of action or are at high risk of complications from the clinical flare seen with LHRH agonists. Abarelix also uniquely caused a sustained decline in serum FSH levels, which have been shown in vitro to stimulate prostate cancer cell growth. If these favorable effects can be duplicated in patients, abarelix might also offer a survival benefit.

=> d l17 14 ibib abs

L17 ANSWER 14 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2007404203 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17616694
TITLE: Combined targeting of endothelin A receptor and epidermal growth factor receptor in ovarian cancer shows enhanced antitumor activity.
AUTHOR: Rosano Laura; Di Castro Valeriana; Spinella Francesca; Tortora Giampaolo; Nicotra Maria Rita; Natali Pier Giorgio; Bagnato Anna
CORPORATE SOURCE: Molecular Pathology Laboratory, Regina Elena Cancer Institute, Rome, Italy.
SOURCE: Cancer research, (2007 Jul 1) Vol. 67, No. 13, pp. 6351-9. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200707
ENTRY DATE: Entered STN: 12 Jul 2007
Last Updated on STN: 28 Jul 2007
Entered Medline: 27 Jul 2007

AB Ovarian carcinomas overexpress endothelin A receptors (ET(A)R) and epidermal growth factor (EGF) receptor (EGFR). In these cells, endothelin-1 (ET-1) triggers mitogenic and invasive signaling pathways that are in part mediated by EGFR transactivation. Combined targeting of ET(A)R, by the specific ET(A)R antagonist ZD4054, and of EGFR by the EGFR inhibitor gefitinib (IRESSA), may offer improvements in ovarian carcinoma treatment. In HEY and OVCA 433 ovarian carcinoma cells, ET-1 or EGF induced rapid activation of EGFR, p42/44 mitogen-activated protein kinase (MAPK), and AKT. ZD4054 was able to reduce the ET-1-induced EGFR transactivation. Gefitinib significantly inhibited EGF- and ET-1-induced EGFR phosphorylation, but incompletely reduced the ET-1-induced activation of downstream targets. ZD4054 plus gefitinib resulted in a greater inhibition of EGFR, MAPK, and AKT phosphorylation, indicating the critical role of these interconnected signaling proteins. ZD4054 effectively inhibited cell proliferation, invasiveness, and vascular endothelial growth factor (VEGF) secretion. Concomitantly, ZD4054 enhanced apoptosis and E-cadherin promoter activity and expression. In both cell lines, the

drug combination resulted in a significant decrease in cell proliferation (65%), invasion (52%), and VEGF production (50%), accompanied by a 2-fold increase in apoptosis. The coadministration of ZD4054 enhanced the efficacy of gefitinib leading to partial (82%) or complete tumor regression on HEY ovarian carcinoma xenografts. Antitumor effects were paralleled by biochemical and immunohistologic evidence of decreased vascularization, Ki-67, matrix metalloproteinase-2 (MMP-2), VEGF, MAPK and EGFR, and enhanced E-cadherin expression. The cross-signaling between the EGFR/ET(A)R pathways provides a rationale to combine EGFR inhibitors with ET(A)R antagonists, identifying new effective therapeutic opportunities for ovarian cancer.

=> d L17 13 ibib abs

L17 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:104606 CAPLUS
DOCUMENT NUMBER: 126:262431
TITLE: Endothelin-1 production and decreased endothelin B receptor expression in advanced prostate cancer
AUTHOR(S): Nelson, Joel B.; Chan-Tack, Kirk; Hedican, Sean P.; Magnuson, Scott R.; Opgenorth, Terry J.; Bova, G. Steve; Simons, Jonathan W.
CORPORATE SOURCE: James Buchanan Brady Urological Inst. Res. Labs., Johns Hopkins Hospital, Baltimore, MD, 21287-2411, USA
SOURCE: Cancer Research (1996), 56(4), 663-8
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The potent vasoconstrictor endothelin-1 (ET-1) is at its highest concentration in the normal human ejaculate and is associated with the progression of metastatic prostate cancer. ET-1 protein expression is detected in situ in 14 of 14 primary cancers and 14 of 16 metastatic sites of human prostatic carcinoma. Exogenous ET-1 induced prostate cancer proliferation directly and enhances the mitogenic effects of insulin-like growth factor I, insulin-like growth factor II, platelet-derived growth factor, basic fibroblast growth factor, and epidermal growth factor in serum-free conditions in vitro. The ETA-selective receptor antagonist A-127722 inhibits ET-1-stimulated growth, but the ETR-selective receptor antagonist BQ-788 does not. ET-3, an ETB-selective agonist, also had no effect on prostate cancer growth. No specific ETB-binding sites could be demonstrated in any established human prostate cancer cell line tested, and ETB mRNA, detected by reverse transcription PCR, was reduced. The predominance of ETB binding on human benign prostatic epithelial tissue is not present in metastatic prostate cancer by autoradiog. In human prostate cancer progression to metastases, ET-1 and ETA expression are retained, whereas ETB receptor expression is reduced.

=> D l17 12 ibib abs

L17 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:227293 CAPLUS
DOCUMENT NUMBER: 126:304398
TITLE: Activation of mitogenic signaling by endothelin 1 in ovarian carcinoma cells
AUTHOR(S): Bagnato, Anna; Tecce, Raffaele; Di Castro, Valeriana; Catt, Kevin J.
CORPORATE SOURCE: Laboratory of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, 00158, Italy
SOURCE: Cancer Research (1997), 57(7), 1306-1311
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Endothelin 1 (ET-1) is produced in ovarian cancer cell lines and has been shown to act through ETA receptors as an autocrine growth factor to promote tumor cell proliferation in vitro. In OVCA 433 cells, the efficacy of ET-1 as a stimulus of [3H]thymidine incorporation was equivalent to that of epidermal growth factor. ET-1 also stimulated the rapid expression of c-fos, an action mediated by ETA receptors. The mitogenic action of ET-1 was not mediated by a pertussis toxin-sensitive G protein. An anal. of the effects of inhibition and depletion of protein kinase C (PKC) on mitogenic responses demonstrated that PKC was necessary but not sufficient for maximal stimulation by ET-1. In quiescent OVCA 433 cells, ET-1-induced stimulation of [3H]thymidine incorporation was prevented by two structurally distinct inhibitors of tyrosine kinase, herbimycin A and genistein. These results indicate that both PKC and protein tyrosine kinase participate in ET-1-stimulated mitogenic signaling. ET-1 rapidly stimulated tyrosine phosphorylation of several cellular proteins among which p125FAK and p42 mitogen-activated protein kinase were identified. The additivity between the potent mitogenic actions of ET-1 and epidermal growth factor is consistent with the independence of their signal transduction pathways in ovarian cancer cells. These findings also indicate that intracellular signaling between the ETA receptor and a yet unidentified tyrosine kinase is involved in the mitogenic response in ET-1.

=> d l17 11 ibib abs

L17 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:75461 CAPLUS
DOCUMENT NUMBER: 130:279913
TITLE: Growth factors and ovarian cancer
AUTHOR(S): Langdon, S. P.; Smyth, J. F.
CORPORATE SOURCE: ICRF Medical Oncology Unit, Western General Hospital, Edinburgh, EH4 2XU, UK
SOURCE: Endocrine-Related Cancer (1998), 5(4), 283-291
CODEN: ERCAE9; ISSN: 1351-0088
PUBLISHER: Society for Endocrinology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 97 refs. Topics discussed include: (1) growth factor families, such as epidermal growth factor -related peptides, transforming growth factor-related-β superfamily, insulin-like growth factor-related-β, endothelins, platelet-derived growth factor, fibroblast growth factor, and other growth factors, and (2)endocrine regulation of growth factors in ovarian cancer.
REFERENCE COUNT: 97 THERE ARE 97 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l17 10 ibib abs

L17 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:702602 CAPLUS
DOCUMENT NUMBER: 134:3338
TITLE: Transactivation of the epidermal growth factor receptor in endothelin-1-induced mitogenic signaling in human ovarian carcinoma cells
AUTHOR(S): Vacca, Fabrizio; Bagnato, Anna; Catt, Kevin J.; Tecce, Raffaele
CORPORATE SOURCE: Laboratory of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, 00158, Italy
SOURCE: Cancer Research (2000), 60(18), 5310-5317

CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Endothelin (ET)-1 is produced in ovarian carcinoma cells and is known to act through ETA receptors as an autocrine growth factor in vitro and in vivo. In OVCA 433 human ovarian carcinoma cells, ET-1 caused phosphorylation of the epidermal growth factor receptor (EGF-R) that was accompanied by phosphorylation of Shc and its recruitment complexed with Grb2. These findings suggested that an EGF-R/ras-dependent pathway may contribute to the activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) 2 and mitogenic signaling induced by ET-1 in these cells. Specific inhibition of EGF-R kinase activity by tyrphostin AG1478 prevented ET-1-induced transactivation of the EGF-R, as well as Shc phosphorylation and recruitment with Grb2. Furthermore, ET-1-induced activation of Erk 2 was partially inhibited by tyrphostin AG1478. In accord with this finding, the mitogenic action of ET-1 in OVCA 433 cells was also significantly reduced by a concentration of tyrphostin AG1478 that abolished the growth response of EGF-stimulated cells. Inhibition of protein kinase C activity, which contributes to the proliferative action of ET-1 in OVCA 433 cells, had no effect on the activation of Erk 2 by ET-1, which suggests that this effect of protein kinase C does not involve ras-independent activation of Erk 2. Inhibition by wortmannin of PI3-kinase activity, which has been implicated in ET-1 and other G protein-coupled receptor (GPCR)-mediated signaling pathways, reduced Erk 2 activation by ET-1 but had no effect on ET-1-induced EGF-R and Shc phosphorylation. These findings indicate that ET-1 -induced stimulation of Erk 2 phosphorylation, and mitogenic responses in OVCA 433 ovarian cancer cells are mediated in part by signaling pathways that are initiated by transactivation of the EGF-R.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l17 9 ibib abs

L17 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:38376 CAPLUS
DOCUMENT NUMBER: 137:4027
TITLE: Endothelin-1 production by prostate cancer cell lines is up-regulated by factors involved in cancer progression and down-regulated by androgens
AUTHOR(S): Granchi, Simone; Brocchi, Sandro; Bonaccorsi, Lorella; Baldi, Elisabetta; Vinci, Maria Cristina; Forti, Gianni; Serio, Mario; Maggi, Mario
CORPORATE SOURCE: Department of Clinical Physiopathology, Unit of Andrology, University of Florence, Florence, Italy
SOURCE: Prostate (New York, NY, United States) (2001), 49(4), 267-277
CODEN: PRSTDS; ISSN: 0270-4137
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent data demonstrate that endothelin-1 (ET-1) concentration increases in plasma of men with advanced, hormone-refractory prostate adenocarcinoma. In addition, ET-1 is involved in osteoblastic remodelling and new bone formation, suggesting a role for this vasoactive peptide in the metastatic progression of prostate cancer to the bone. We investigated the regulation of ET-1 expression in androgen-sensitive and insensitive prostate cancer cell lines by androgens and several factors involved in progression of prostate cancer (EGF) and bone remodelling (TGFβ-1, IL1-α and IGF-1). Northern anal. and radio immunoassay demonstrated that all the ET-1 pathways are tuned off in the androgen-sensitive LNCaP cell line when

compared to the androgen-insensitive PC-3 and DU145. In PC-3 cells transfected with a full-length androgen receptor expression vector (PC-3-AR), treatment with androgens reduced gene expression and secretion of ET-1 without affecting the gene expression of ET-3. Collectively, these data support a role for androgens in the regulation of ET-1 production by prostate adenocarcinoma cells. In PC-3 and DU145 cells, ET-1 gene expression and secretion were up-regulated by TGFβ-1, EGF and IL1-α, whereas IGF-1 was ineffective. Conversely, none of the treatments affected ECE-1 or ET-3 gene expression. In conclusion, ET-1 production by prostate adenocarcinoma cells is down-regulated by androgens and up-regulated by factors involved in tumor progression indicating a role for this peptide in the biol. of prostate cancer. In view of the role exerted by ET-1 in the process of bone metastasis, our data suggest the use of ET-1 receptor antagonists in the treatment of advanced prostate cancer.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l17 8 ibib abs

L17 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:354796 CAPLUS
DOCUMENT NUMBER: 140:368653
TITLE: Endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for the treatment of cancer
INVENTOR(S): Boyle, Francis Thomas; Curwen, Jon Owen; Gallagher, Neil James; Hancox, Ursula Joy; Hughes, Andrew Mark; Johnstone, Donna; Taylor, Sian Tomiko; Tonge, David William
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035057	A1	20040429	WO 2003-GB4347	20031007
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2501959	A1	20040429	CA 2003-2501959	20031007
AU 2003269259	A1	20040504	AU 2003-269259	20031007
AU 2003269259	B2	20070315		
EP 1553950	A1	20050720	EP 2003-751038	20031007
EP 1553950	B1	20070808		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003015140	A	20050816	BR 2003-15140	20031007
CN 1703224	A	20051130	CN 2003-80101310	20031007
JP 2006510605	T	20060330	JP 2004-544431	20031007
AT 369136	T	20070815	AT 2003-751038	20031007
NO 2005001658	A	20050506	NO 2005-1658	20050404
MX 2005PA03808	A	20050608	MX 2005-PA3808	20050408

ZA 2005002874	A	20060222	ZA 2005-2874		20050408
US 2006122180	A1	20060608	US 2005-530794		20050408
PRIORITY APPLN. INFO.:			GB 2002-23854	A	20021012
			WO 2003-GB4347	W	20031007

AB A combination, comprising an endothelin receptor antagonist (e.g. ZD4054), or a pharmaceutically acceptable salt thereof, and an EGF receptor tyrosine kinase inhibitor (e.g. ZD1839), or a pharmaceutically acceptable salt thereof, is described. The combination of the invention is useful for the treatment of cancer, e.g. prostate cancer.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l17 7 ibib abs

L17 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:453395 CAPLUS

DOCUMENT NUMBER: 141:21838

TITLE: Gene expression profiling in epidermal growth factor receptor-positive cancers and its use in prognosis and selection of therapies

INVENTOR(S): Baker, Joffre B.; Cronin, Maureen T.; Shak, Steven; Baselga, Jose

PATENT ASSIGNEE(S): Genomic Health, Inc., USA; Vall D'hebron University Hospital

SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004046386	A1	20040603	WO 2003-US36777		20031114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2506066	A1	20040603	CA 2003-2506066		20031114
AU 2003295598	A1	20040615	AU 2003-295598		20031114
US 2005019785	A1	20050127	US 2003-714195		20031114
EP 1570080	A1	20050907	EP 2003-786796		20031114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2006506093	T	20060223	JP 2004-553847		20031114
PRIORITY APPLN. INFO.:			US 2002-427090P	P	20021115
			WO 2003-US36777	W	20031114

AB Genes that show altered patterns of expression in cancers where the epidermal growth factor receptor (EGFR) is present are identified for use in selection of therapeutic regimens and in prognosis of the disease. The gene expression profiles determined using paraffin-embedded, fixed tissue samples of EGFR-pos. cancer allow a physician to predict whether a patient is likely to respond well to treatment with an EGFR inhibitor.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l17 6 ibib abs

L17 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:38448 CAPLUS
DOCUMENT NUMBER: 142:152954
TITLE: Endothelin-1 stimulates cyclooxygenase-2 expression in ovarian cancer cells through multiple signaling pathways: Evidence for involvement of transactivation of the epidermal growth factor receptor
AUTHOR(S): Spinella, Francesca; Rosano, Laura; Elia, Giacomo; Di Castro, Valeriana; Natali, Pier Giorgio; Bagnato, Anna
CORPORATE SOURCE: Laboratories of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, Italy
SOURCE: Journal of Cardiovascular Pharmacology (2004), 44(Suppl. 1), S140-S143
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ovarian carcinoma cells release high amts. of endothelin-1 and exhibit increased expression of endothelin-A receptor. Engagement of the endothelin-A receptor triggers tumor growth, survival, neoangiogenesis and invasion. Cyclooxygenase-1 and cyclooxygenase-2 are enzymes involved in the production of prostaglandins and play a role in the regulation of tumor progression in several malignancies, including ovarian carcinomas. Endothelin-1 significantly increases the expression of cyclooxygenase-1 and cyclooxygenase-2 mRNA and protein, the activity of the cyclooxygenase-2 promoter, and the release of prostaglandin E2 from two ovarian carcinoma cell lines, HEY and OVCA 433. The cyclooxygenase-2 inhibitor, NS-398 drastically decreased the endothelin-1-induced prostaglandin E2 production and vascular endothelial growth factor upregulation, indicating a role for cyclooxygenase-2 in endothelin-1-induced vascular endothelial growth factor-mediated angiogenesis. In this study the authors demonstrated that endothelin-1-induced cyclooxygenase-2 and related prostaglandin E2 release were dependent upon the activation of endothelin-A receptor and of multiple mitogen-activated protein kinase signal pathways, including extracellular signal-regulated kinase 1/2 kinase, p38 mitogen-activated protein kinase and the transactivation of the epidermal growth factor receptor. In human ovarian xenografts, the levels of cyclooxygenase-2 protein expression were significantly reduced following treatment with the endothelin-A receptor selective antagonist, atrasentan, compared with untreated mice. These results suggest that the pharmacol. blocking of endothelin-A receptor is an attractive strategy to control the cyclooxygenase-2 protein expression in ovarian carcinoma.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l17 5 ibib abs

L17 ANSWER 5 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:313416 CAPLUS
DOCUMENT NUMBER: 143:70824
TITLE: Newer therapies in advanced prostate cancer
AUTHOR(S): Hegeman, Robert B.; Liu, Glenn; Wilding, George; McNeel, Douglas G.
CORPORATE SOURCE: University of Wisconsin Comprehensive Cancer Center, Madison, USA
SOURCE: Clinical Prostate Cancer (2004), 3(3), 150-156
CODEN: CPCLC4; ISSN: 1540-0352
PUBLISHER: Cancer Information Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Prostate cancer is a leading cause of morbidity and mortality among males. Androgen ablation as initial therapy for advanced prostate cancer provides high response rates but does not cure disease, as nearly all men with metastases will eventually progress to hormone-refractory prostate cancer (HRPC). Present chemotherapy regimens for HRPC can provide palliation and have recently demonstrated an increase in overall survival. Over the past 2 decades, these regimens represent clear advances in the treatment of metastatic prostate cancer but also demonstrate that newer therapies are needed. Studies are ongoing to provide viable alternatives among traditional cytotoxic therapies as well as among novel agents targeting specific mol. pathways. This article reviews some of the newer therapies being developed and evaluated, including the epothilone analogs, human epidermal growth factor receptor pathway inhibitors, angiogenesis inhibitors, and endothelin receptor antagonists.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l17 ibib abs

L17 ANSWER 1 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:748964 CAPLUS

TITLE: Combined targeting of endothelin A receptor and epidermal growth factor receptor in ovarian cancer shows enhanced antitumor activity

AUTHOR(S): Rosano, Laura; Di Castro, Valeriana; Spinella, Francesca; Tortora, Giampaolo; Nicotra, Maria Rita; Natali, Pier Giorgio; Bagnato, Anna

CORPORATE SOURCE: Molecular Pathology and Immunology Laboratories, Regina Elena Cancer Institute, Institute of Molecular Biology and Pathology, National Research Council, Rome, Endocrinology and Molecular Oncology Department, University of Naples, Federico II, Naples, Italy

SOURCE: Cancer Research (2007), 67(13), 6351-6359
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Ovarian carcinomas overexpress endothelin A receptors (ETAR) and epidermal growth factor (EGF) receptor (EGFR). In these cells, endothelin-1 (ET-1) triggers mitogenic and invasive signaling pathways that are in part mediated by EGFR transactivation. Combined targeting of ETAR, by the specific ETAR antagonist ZD4054, and of EGFR by the EGFR inhibitor gefitinib (IRESSA), may offer improvements in ovarian carcinoma treatment. In HEY and OVCA 433 ovarian carcinoma cells, ET-1 or EGF induced rapid activation of EGFR, p42/44 mitogen-activated protein kinase (MAPK), and AKT. ZD4054 was able to reduce the ET-1-induced EGFR transactivation. Gefitinib significantly inhibited EGF- and ET-1-induced EGFR phosphorylation, but incompletely reduced the ET-1-induced activation of downstream targets. ZD4054 plus gefitinib resulted in a greater inhibition of EGFR, MAPK, and AKT phosphorylation, indicating the critical role of these interconnected signaling proteins. ZD4054 effectively inhibited cell proliferation, invasiveness, and vascular endothelial growth factor (VEGF) secretion. Concomitantly, ZD4054 enhanced apoptosis and E-cadherin promoter activity and expression. In both cell lines, the drug combination resulted in a significant decrease in cell proliferation (65%), invasion (52%), and VEGF production (50%), accompanied by a 2-fold increase in apoptosis. The coadministration of ZD4054 enhanced the efficacy of gefitinib leading to partial (82%) or complete tumor regression on HEY ovarian carcinoma xenografts. Antitumor effects were paralleled by biochem. and immunohistol. evidence of decreased vascularization, Ki-67, matrix metalloproteinase-2 (MMP-2), VEGF, MAPK and EGFR, and enhanced E-cadherin expression. The cross-signaling between the

EGFR/ETAR pathways provides a rationale to combine EGFR inhibitors with ETAR antagonists, identifying new effective therapeutic opportunities for ovarian cancer.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l17 2 ibib abs

L17 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:194557 CAPLUS
TITLE: Mechanisms of endothelin 1-stimulated proliferation in colorectal cancer cell lines
AUTHOR(S): Grant, K.; Knowles, J.; Dawas, K.; Burnstock, G.; Taylor, I.; Loizidou, M.
CORPORATE SOURCE: Department of Surgery, Royal Free and University College Medical School, University College London, London, UK
SOURCE: British Journal of Surgery (2007), 94(1), 106-112
CODEN: BJSUAM; ISSN: 0007-1323
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: The peptide endothelin (ET) 1 promotes proliferation in a number of epithelial cancers. The aim of this study was to identify the mechanism of ET-1-stimulated proliferation in colorectal cancer cells in vitro. Methods: The effects of ET-1 on colorectal cancer cell lines HT29, LIM1215 and SW620 were studied. Cells were cultured with ET-1 plus antagonists/inhibitors to ETA or ETB receptors, G protein subtypes, phosphoinositide 3-kinase (PI3K) or protein kinase C (PKC). DNA replication and apoptosis were investigated by 5-bromo-2'-deoxyuridine incorporation and Annexin V staining. Transactivation of the epidermal growth factor (EGF) receptor was investigated by blockade of the receptor in the presence of ET-1, measurement of levels of phosphorylated EGF receptor in the presence of ET-1, and comparing the effects of ET-1 and EGF on cell proliferation. Results: ET-1 significantly stimulated growth of all cell lines via ETA receptors. ET-1 stimulated DNA replication, not apoptosis. ET-1-stimulated growth was inhibited by antagonism of pertussis toxin-sensitive G proteins, PI3K and PKC. Inhibition of the EGF receptor reduced the effect of ET-1. ET-1 increased levels of phosphorylated EGF receptor via the ETA receptor. Conclusion: ET-1 increased DNA replication in colorectal cancer cells via the ETA receptor. This mitogenic action was mediated via pertussis toxin-sensitive G proteins, PI3K, PKC and transactivation of the EGF receptor.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 08:18:45 ON 06 SEP 2007)

FILE 'CAPLUS, MEDLINE' ENTERED AT 08:22:28 ON 06 SEP 2007
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L2 4 S L1 AND LUNG CANCER
L3 411 S L1 AND (PY<2003 OR AY<2003 OR PRY<2003)
L4 476 S ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR
L5 12 S L3 AND L4
L6 71 S ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) AND (EGF OR EGFR
L7 5 S L3 AND L6
L8 5 S L5 AND L7
L9 0 S L4 AND LUNG CANCER
L10 0 S L6 AND LUNG CANCER
L11 45 S L4 AND CANCER
L12 8 S L6 AND CANCER

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L13          71 S L4 AND L6
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L15          33 S L3 AND CANCER
L16           1 S L3 AND LUNG CANCER
L17          22 S ((ENDOTHELIN OR ET1 OR ET 1 OR ET-1 OR ETAR) (S) (EGF OR EGFR

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LOGOFF? (Y)/N/HOLD:y
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FULL ESTIMATED COST                                     247.79     249.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                     -24.18     -24.18

STN INTERNATIONAL LOGOFF AT 09:22:22 ON 06 SEP 2007
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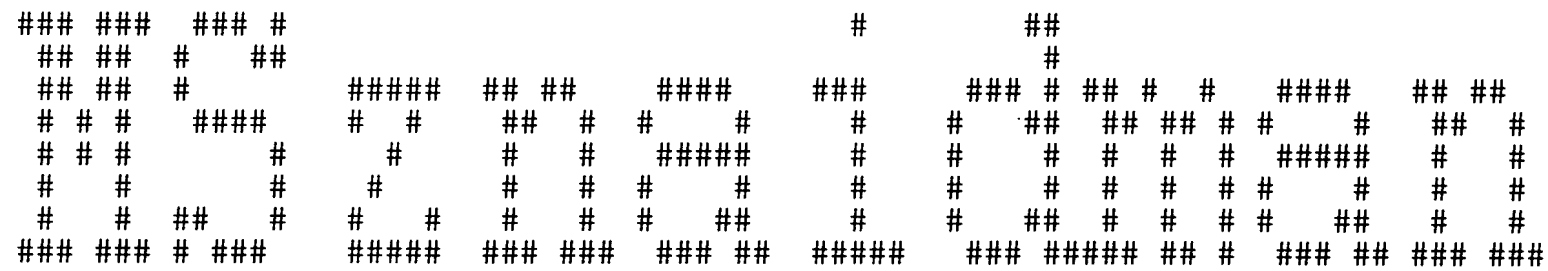

Job : 220
Date: 9/6/2007
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LOGINID:SSPTAMLS1614

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NEWS	3	MAY 08	CA/CAplus Indian patent publication number format defined
NEWS	4	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
NEWS	5	MAY 21	BIOSIS reloaded and enhanced with archival data
NEWS	6	MAY 21	TOXCENTER enhanced with BIOSIS reload
NEWS	7	MAY 21	CA/CAplus enhanced with additional kind codes for German patents
NEWS	8	MAY 22	CA/CAplus enhanced with IPC reclassification in Japanese patents
NEWS	9	JUN 27	CA/CAplus enhanced with pre-1967 CAS Registry Numbers
NEWS	10	JUN 29	STN Viewer now available
NEWS	11	JUN 29	STN Express, Version 8.2, now available
NEWS	12	JUL 02	LEMBASE coverage updated
NEWS	13	JUL 02	LMEDLINE coverage updated
NEWS	14	JUL 02	SCISEARCH enhanced with complete author names
NEWS	15	JUL 02	CHEMCATS accession numbers revised
NEWS	16	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS	17	JUL 16	CAplus enhanced with French and German abstracts
NEWS	18	JUL 18	CA/CAplus patent coverage enhanced
NEWS	19	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS	20	JUL 30	USGENE now available on STN
NEWS	21	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS	22	AUG 06	BEILSTEIN updated with new compounds
NEWS	23	AUG 06	FSTA enhanced with new thesaurus edition
NEWS	24	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS	25	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS	26	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS	27	AUG 27	USPATOLD now available on STN
NEWS	28	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data

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CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

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FILE 'HOME' ENTERED AT 09:51:35 ON 06 SEP 2007

=> File caplus medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

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=> s 186497-07-4/RN
'RN' IS NOT A VALID FIELD CODE
L1 20 186497-07-4/RN

=> file registry

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.74	5.95

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DICTIONARY FILE UPDATES: 5 SEP 2007 HIGHEST RN 946114-43-8

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E6	1	ZD4R/BI
E7	3	ZD5/BI
E8	6	ZD52F10/BI
E9	1	ZD54H05/BI
E10	1	ZD582/BI
E11	1	ZD5C/BI

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E12             1     ZD5R/BI

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must be in the range 5-25.

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E10             1     ZD 4974/CN
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E12             1     ZD 5522/CN

=> S E3
L2              1 "ZD 4054"/CN

=> D L2

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   186497-07-4  REGISTRY
ED   Entered STN:  27 Feb 1997
CN   3-Pyridinesulfonamide, N-(3-methoxy-5-methyl-2-pyrazinyl)-2-[4-(1,3,4-
     oxadiazol-2-yl)phenyl]-  (CA INDEX NAME)
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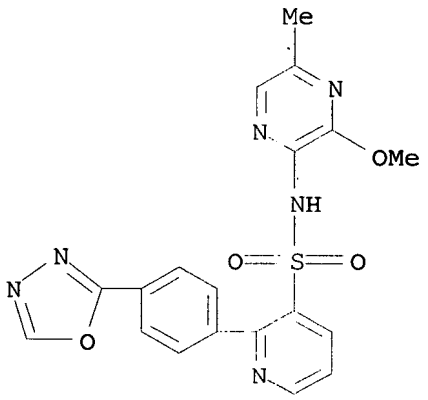

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

18 REFERENCES IN FILE CA (1907 TO DATE)
20 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> File caplus medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.80	13.75

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FILE 'MEDLINE' ENTERED AT 09:55:57 ON 06 SEP 2007

=> S L2
L3 20 L2

=> D L2 20 ibib abs
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:n

=> D L3 20 ibib abs

L3 ANSWER 20 OF 20 CAPLUS
ACCESSION NUMBER: 1997:132770 CAPLUS
DOCUMENT NUMBER: 126:144291
TITLE: N-pyrazinyl-2-phenyl-3-pyridinesulfonamides and analogs endothelin receptor antagonists
INVENTOR(S): Bradbury, Robert Hugh; Butlin, Roger John; James, Roger
PATENT ASSIGNEE(S): Zeneca Limited, UK
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640681	A1	19961219	WO 1996-GB1295	19960603
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RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
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AU 9658403	A	19961230	AU 1996-58403	19960603
AU 715041	B2	20000113		
EP 832082	A1	19980401	EP 1996-919941	19960603
EP 832082	B1	20011121		
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CN 1192739	A	19980909	CN 1996-196149	19960603
CN 1097051	B	20021225		
BR 9608611	A	19990511	BR 1996-8611	19960603
JP 11509175	T	19990817	JP 1997-500209	19960603
JP 3193058	B2	20010730		
HU 9802300	A2	19991028	HU 1998-2300	19960603
NZ 308619	A	20000128	NZ 1996-308619	19960603
RU 2172738	C2	20010827	RU 1998-100054	19960603

AT 209200	T	20011215	AT 1996-919941		19960603
SK 282338	B6	20020107	SK 1997-1680		19960603
CZ 289387	B6	20020116	CZ 1997-3887		19960603
PT 832082	T	20020429	PT 1996-919941		19960603
IL 122464	A	20020523	IL 1996-122464		19960603
ES 2168487	T3	20020616	ES 1996-919941		19960603
PL 187897	B1	20041029	PL 1996-324660		19960603
ZA 9604615	A	19961209	ZA 1996-4615		19960604
US 5866568	A	19990202	US 1996-658969		19960604
IN 1996DE01209	A	20050311	IN 1996-DE1209		19960604
HR 960272	B1	20060630	HR 1996-272		19960606
NO 9705700	A	19971205	NO 1997-5700		19971205
NO 314503	B1	20030331			
HK 1005801	A1	20021220	HK 1998-105010		19980606
US 6060475	A	20000509	US 1998-211483		19981214
US 6258817	B1	20010710	US 2000-504364		20000215
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			GB 1995-19666	A	19950927
			WO 1996-GB1295	W	19960603
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OTHER SOURCE(S): MARPAT 126:144291

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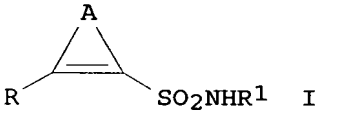

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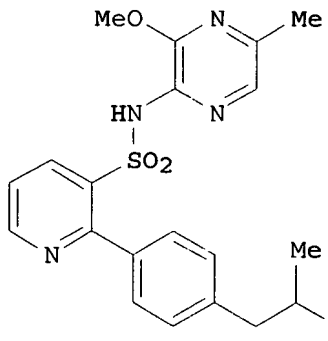

II

AB Title compds. [I; A = atoms to complete an (un)substituted pyridine ring; R = (un)substituted Ph; R1 = (un)substituted heteroarom. ring containing 2 N atoms] were prepared Thus, iso-Bu N-(3-methoxy-5-methyl-2-pyrazinyl)carbamate was amidated by 2-chloropyridine-3-sulfonyl chloride (preparation each given) and the product arylated by 4-(Me2CHCH2)C6H4B(OH)2 to give, after deprotection, title compound II. Data for biol activity of I were given.

=> D l3 19 ibib abs

L3 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2004:182737 CAPLUS
DOCUMENT NUMBER:	140:210754
TITLE:	Therapeutic use of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide
INVENTOR(S):	Tonge, David William; Taylor, Sian Tomiko; Boyle, Francis Thomas; Hughes, Andrew Mark; Johnstone, Donna; Ashford, Marianne Bernice; Barrass, Nigel Charles
PATENT ASSIGNEE(S):	Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE:	PCT Int. Appl., 23 pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004018044	A2	20040304	WO 2003-GB3653	20030820
WO 2004018044	A3	20040506		
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AU 2003255835	B2	20070405		
BR 2003013655	A	20050621	BR 2003-13655	20030820
EP 1545710	A2	20050629	EP 2003-792501	20030820
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JP 2004083590	A	20040318	JP 2003-299605	20030825
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NO 2005000689	A	20050321	NO 2005-689	20050209
MX 2005PA01862	A	20050603	MX 2005-PA1862	20050216
US 2006094729	A1	20060504	US 2005-524963	20050218
AU 2007203079	A1	20070719	AU 2007-203079	20070702

PRIORITY APPLN. INFO.:

GB 2002-19660	A	20020823
AU 2003-255835	A3	20030820
WO 2003-GB3653	W	20030820
JP 2003-299605	A3	20030825

AB The use of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide, or a pharmaceutically acceptable salt thereof, in the treatment of cancer and/or pain in a warm blooded animal such as man is described.

=> d l3 18 ibib abs

L3 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:331974 CAPLUS
DOCUMENT NUMBER: 140:332519
TITLE: 5-HT1B/1D receptor agonists for the treatment of headache resulting from administering an endothelin receptor antagonist
INVENTOR(S): Curwen, Jon Owen; Hughes, Andrew Mark; Johnstone, Donna; Morris, Clive Dylan
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca Uk Limited
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004032922	A1	20040422	WO 2003-GB4338	20031006

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    AU 2003274307        A1    20040504    AU 2003-274307          20031006
    EP 1551395           A1    20050713    EP 2003-758297          20031006
    EP 1551395           B1    20070711
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
    JP 2006508933        T     20060316    JP 2004-542622          20031006
    AT 366572            T     20070815    AT 2003-758297          20031006
    US 2006009512        A1    20060112    US 2005-530232          20050404
PRIORITY APPLN. INFO.:                       GB 2002-23367       A  20021009
                                             WO 2003-GB4338      W  20031006
AB  The invention discloses the use of a 5-HT1B/1D receptor agonist in the
    treatment or prevention of headache that results from administering an
    endothelin receptor antagonist.  The invention also discloses a
    combination comprising an endothelin receptor antagonist and a 5-HT1B/1D
    receptor agonist.
REFERENCE COUNT:          1     THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> D l3 17 ibib abs

L3   ANSWER 17 OF 20  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:354796  CAPLUS
DOCUMENT NUMBER:          140:368653
TITLE:                    Endothelin receptor antagonist-EGF receptor tyrosine
                          kinase inhibitor combination for the treatment of
                          cancer
INVENTOR(S):              Boyle, Francis Thomas; Curwen, Jon Owen; Gallagher,
                          Neil James; Hancox, Ursula Joy; Hughes, Andrew Mark;
                          Johnstone, Donna; Taylor, Sian Tomiko; Tonge, David
                          William
PATENT ASSIGNEE(S):       Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE:                   PCT Int. Appl., 24 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

    PATENT NO.            KIND   DATE        APPLICATION NO.         DATE
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    WO 2004035057          A1    20040429    WO 2003-GB4347          20031007
        W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
            GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
            LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
            OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
            TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
            KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
            FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
            BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
    CA 2501959             A1    20040429    CA 2003-2501959         20031007
    AU 2003269259          A1    20040504    AU 2003-269259          20031007
    AU 2003269259          B2    20070315
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EP 1553950	A1	20050720	EP 2003-751038		20031007
EP 1553950	B1	20070808			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003015140	A	20050816	BR 2003-15140		20031007
CN 1703224	A	20051130	CN 2003-80101310		20031007
JP 2006510605	T	20060330	JP 2004-544431		20031007
AT 369136	T	20070815	AT 2003-751038		20031007
NO 2005001658	A	20050506	NO 2005-1658		20050404
MX 2005PA03808	A	20050608	MX 2005-PA3808		20050408
ZA 2005002874	A	20060222	ZA 2005-2874		20050408
US 2006122180	A1	20060608	US 2005-530794		20050408
PRIORITY APPLN. INFO.:			GB 2002-23854	A	20021012
			WO 2003-GB4347	W	20031007

AB A combination, comprising an endothelin receptor antagonist (e.g. ZD4054), or a pharmaceutically acceptable salt thereof, and an EGF receptor tyrosine kinase inhibitor (e.g. ZD1839), or a pharmaceutically acceptable salt thereof, is described. The combination of the invention is useful for the treatment of cancer, e.g. prostate cancer.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D l3 16 ibib abs

L3 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:800517 CAPLUS

DOCUMENT NUMBER: 142:166029

TITLE: N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridine-3-sulfonamide (ZD4054 Form 1)

AUTHOR(S): Stensland, Birgitta; Roberts, Ron J.

CORPORATE SOURCE: Preformulation and Biopharmaceutics, Solid State Analysis and Physical Chemistry, AstraZeneca PAR&D/SBBG B341:3, Soedertaelje, SE-151 85, Swed.

SOURCE: Acta Crystallographica, Section E: Structure Reports Online (2004), E60(10), o1817-o1819
CODEN: ACSEBH; ISSN: 1600-5368
URL: http://journals.iucr.org/e/graphics/htmlborder.gif

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB The title compound, C19H16N6O4S, crystallizes from N-methylpyridine in the centrosym. space group P21/n with Z = 4. Crystallog. data are given. The mol. has 11 heteroatoms, of which only one is protonated. This potential H-bond donor, viz. the NH amide group, participates in both intra- and intermol. H-bond interactions, thus contributing to the stabilization of the mol. conformation and the linking of mols. as dimers. The hairpin-like folded mol. is arranged with three of its four aromatic rings in two parallel planes intersected by a sulfonamide moiety. In this way, the mols. stack efficiently, facilitated by short-range van der Waals forces. No residual volume for solvent inclusion was found.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D l3 15 ibib abs

L3 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:232622 CAPLUS

DOCUMENT NUMBER: 142:303627

TITLE: Combination comprising n-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and an LHRH analog and/or a

bisphosphonate
INVENTOR(S): Gallagher, Neil
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005023264	A1	20050317	WO 2004-GB3733	20040902
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004269956	A1	20050317	AU 2004-269956	20040902
CA 2537096	A1	20050317	CA 2004-2537096	20040902
EP 1663236	A1	20060607	EP 2004-768282	20040902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004013974	A	20061031	BR 2004-13974	20040902
CN 1878555	A	20061213	CN 2004-80032911	20040902
JP 2007504265	T	20070301	JP 2006-525875	20040902
US 2006287241	A1	20061221	US 2006-569583	20060223
NO 2006001051	A	20060403	NO 2006-1051	20060303
MX 2006PA02485	A	20060620	MX 2006-PA2485	20060303
IN 2006DN01692	A	20070323	IN 2006-DN1692	20060328
PRIORITY APPLN. INFO.:			GB 2003-20806 A	20030905
			WO 2004-GB3733 W	20040902

AB A combination, comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide, or a pharmaceutically acceptable salt thereof, and an LHRH analog and / or a bisphosphonate is described.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D l3 14 ibib abs

L3 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:283298 CAPLUS
DOCUMENT NUMBER: 142:349042
TITLE: Combinations of chlorpromazine compounds and antiproliferative drugs for the treatment of neoplasms
INVENTOR(S): Lee, Margaret S.; Nichols, James M.; Zhang, Yanzhen; Keith, Curtis
PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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     WO 2005027842         A2    20050331    WO 2004-US30368        20040916
     WO 2005027842         A3    20051222
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
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     US 2004154316         A1    20040812    US 2003-359834         20030207
     CA 2515188            A1    20040826    CA 2004-2515188        20040203
     WO 2004072913         A2    20040826    WO 2004-US3021         20040203
     WO 2004072913         A3    20041111
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     EP 1590776            A2    20051102    EP 2004-707767         20040203
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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     BR 2004007281         A     20060131    BR 2004-7281           20040203
     CN 1754192            A     20060329    CN 2004-80005053       20040203
     AU 2004273910         A1    20050331    AU 2004-273910         20040916
     CA 2538570            A1    20050331    CA 2004-2538570        20040916
     EP 1670477            A2    20060621    EP 2004-788798         20040916
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR
     BR 2004014568         A     20061107    BR 2004-14568          20040916
     CN 1878556            A     20061213    CN 2004-80033294       20040916
     JP 2007505914         T     20070315    JP 2006-527024         20040916
     MX 2005PA08325        A     20060228    MX 2005-PA8325         20050805
     MX 2006PA03066        A     20060620    MX 2006-PA3066         20060317
     NO 2006001325         A     20060606    NO 2006-1325           20060323
PRIORITY APPLN. INFO.:                        US 2003-504310P     P  20030918
                                              US 2003-359834      A  20030207
                                              WO 2004-US3021      W  20040203
                                              WO 2004-US30368     W  20040916

OTHER SOURCE(S):          MARPAT 142:349042
AB   The invention discloses a method for treating a patient having a cancer or
     other neoplasm by administering chlorpromazine or a chlorpromazine analog
     and an antiproliferative agent simultaneously or within 14 days of each
     other in amts. sufficient to treat the patient.


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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
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FULL ESTIMATED COST                                     30.87      44.62

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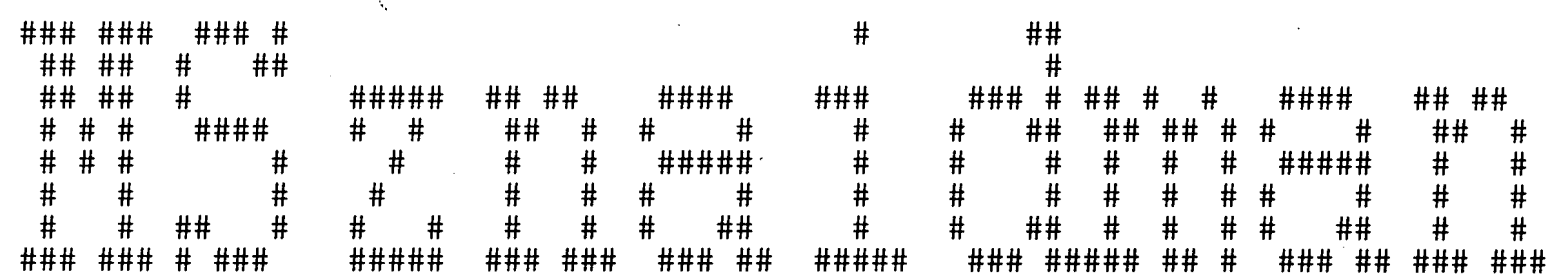

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Date: 9/6/2007
Time: 2:30:48 PM

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NEWS 3	MAY 08	CA/CAplus Indian patent publication number format defined
NEWS 4	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
NEWS 5	MAY 21	BIOSIS reloaded and enhanced with archival data
NEWS 6	MAY 21	TOXCENTER enhanced with BIOSIS reload
NEWS 7	MAY 21	CA/CAplus enhanced with additional kind codes for German patents
NEWS 8	MAY 22	CA/CAplus enhanced with IPC reclassification in Japanese patents
NEWS 9	JUN 27	CA/CAplus enhanced with pre-1967 CAS Registry Numbers
NEWS 10	JUN 29	STN Viewer now available
NEWS 11	JUN 29	STN Express, Version 8.2, now available
NEWS 12	JUL 02	LEMBASE coverage updated
NEWS 13	JUL 02	LMEDLINE coverage updated
NEWS 14	JUL 02	SCISEARCH enhanced with complete author names
NEWS 15	JUL 02	CHEMCATS accession numbers revised
NEWS 16	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 17	JUL 16	CAplus enhanced with French and German abstracts
NEWS 18	JUL 18	CA/CAplus patent coverage enhanced
NEWS 19	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 20	JUL 30	USGENE now available on STN
NEWS 21	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 22	AUG 06	BEILSTEIN updated with new compounds
NEWS 23	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 24	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 25	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 26	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 27	AUG 27	USPATOLD now available on STN
NEWS 28	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data

NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

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NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

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FILE 'HOME' ENTERED AT 11:26:28 ON 06 SEP 2007

=> File registry
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 11:26:43 ON 06 SEP 2007
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DICTIONARY FILE UPDATES: 5 SEP 2007 HIGHEST RN 946114-43-8

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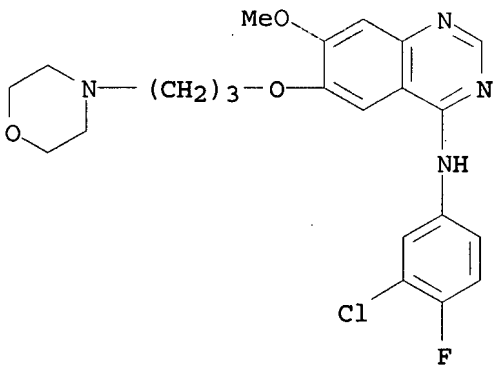
http://www.cas.org/support/stngen/stndoc/properties.html

=> S ZD 1839/CN
L1 1 ZD 1839/CN

=> D L1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 184475-35-2 REGISTRY
ED Entered STN: 26 Dec 1996
CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)
OTHER NAMES:
CN (3-Chloro-4-fluorophenyl)[7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-yl]amine
CN 4-(3'-Chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline
CN Gefitinib
CN Iressa
CN ZD 1839
MF C22 H24 Cl F N4 O3
CI COM
SR CA
LC STN Files: ADISINSIGHT, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CSCHEM, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1446 REFERENCES IN FILE CA (1907 TO DATE)
7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1458 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.35	7.56

FILE 'CAPLUS' ENTERED AT 11:27:28 ON 06 SEP 2007
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 6 Sep 2007 VOL 147 ISS 11
FILE LAST UPDATED: 5 Sep 2007 (20070905/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s L1
L2 1458 L1

=> S Zeneca/cs
L3 2839 ZENECA/CS

=> s L1 and L2
1458 L1
L4 1458 L1 AND L2

=> S L1 and (EGF inhibitor or EGFR inhibitor)

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          1458 L1
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            48 EGFS
         27808 EGF
                 (EGF OR EGFS)
        549956 INHIBITOR
        553709 INHIBITORS
        863748 INHIBITOR
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            37 EGF INHIBITOR
                 (EGF(W)INHIBITOR)
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          9113 EGFR
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        553709 INHIBITORS
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L6           11 L5 AND PY<2003

=> d l6 1-11 ibib abs

L6   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2002:924064  CAPLUS
DOCUMENT NUMBER:          139:111160
TITLE:                    Phase I safety, pharmacokinetic, and pharmacodynamic
                          trial of ZD1839, a selective oral epidermal growth
                          factor receptor tyrosine kinase inhibitor, in patients
                          with five selected solid tumor
AUTHOR(S):                Baselga, J.; Rischin, D.; Ranson, M.; Calvert, H.;
                          Raymond, E.; Kieback, D. G.; Kaye, S. B.; Gianni, L.;
                          Harris, A.; Bjork, T.; Averbuch, S. D.; Feyereislova,
                          A.; Swaisland, H.; Rojo, F.; Albanell, J.
CORPORATE SOURCE:         Vall d'Hebron University Hospital, Barcelona, Spain
SOURCE:                   Journal of Clinical Oncology (2002), 20(21),
                          4292-4302
                          CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER:                Lippincott Williams & Wilkins
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   To establish the safety and tolerability of ZD1839 (Iressa), a selective
     epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, and to
     explore its pharmacokinetic and pharmacodynamic effects in patients with
     selected solid tumor types.
REFERENCE COUNT:          43    THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 2 OF 11  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2002:777929  CAPLUS
DOCUMENT NUMBER:          137:294954
TITLE:                    Preparation of 2-(4-substituted-2-oxo-1,2-
                          dihydropyridin-3-yl)-benzimidazoles as novel tyrosine
                          kinase inhibitors
INVENTOR(S):              Wittman, Mark D.; Balasubramanian, Neelakantan;
                          Velaparthi, Upender; Zimmermann, Kurt; Saulnier, Mark
                          G.; Liu, Peiying; Sang, Xiaopeng; Frennesson, David
                          B.; Stoffan, Karen M.; Tarrant, James G.
PATENT ASSIGNEE(S):       Bristol-Myers Squibb Company, USA
```
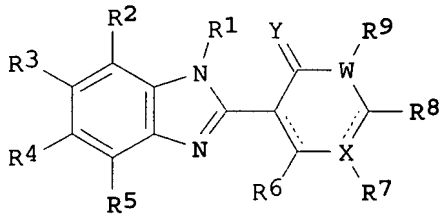
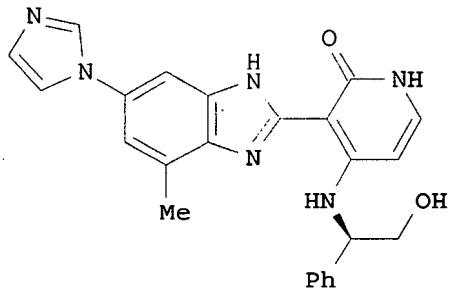

SOURCE: PCT Int. Appl., 249 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 2002079192	A1	20021010	WO 2002-US9402		20020326	<--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW						
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG						
CA 2442428	A1	20021010	CA 2002-2442428		20020326	<--
AU 2002254399	A1	20021015	AU 2002-254399		20020326	<--
EP 1381598	A1	20040121	EP 2002-723631		20020326	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR						
EE 200300475	A	20040216	EE 2003-475		20020326	
CN 1514833	A	20040721	CN 2002-810516		20020326	
JP 2004534010	T	20041111	JP 2002-577817		20020326	
BR 2002008373	A	20050222	BR 2002-8373		20020326	
HU 200400323	A2	20051128	HU 2004-323		20020326	
MX 2003PA08690	A	20031212	MX 2003-PA8690		20030924	
ZA 2003007466	A	20050113	ZA 2003-7466		20030925	
NO 2003004308	A	20031126	NO 2003-4308		20030926	
BG 108206	A	20041130	BG 2003-108206		20030926	
IN 2003DN01548	A	20070316	IN 2003-DN1548		20030926	
PRIORITY APPLN. INFO.:			US 2001-279327P	P	20010328	
			WO 2002-US9402	W	20020326	

OTHER SOURCE(S): MARPAT 137:294954
GI



I



II

AB The title compds. [I; X = N, C, a bond, etc.; Y = O, S; W = N, C, O, S (if W = O or S, then R9 is absent); R1-R9 = H, alkyl, cycloalkyl, etc.] and their pharmaceutically acceptable salts which inhibit tyrosine kinase enzymes thereby making them useful as anti-cancer agents, were prepared Thus, reacting 3-[6-(imidazol-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-iodo-1H-pyridin-2-one (preparation given) with (S)-(-)-2-phenylglycinol in the presence of N-methylmorpholine in DMF afforded 52% (S)-II which showed IC50 of 1.0 μM in cytotoxicity assay (HT-29 human colon tumor cell line). 30 Of the exemplified compds. I showed kinase activity of <25μM against one or more of the following kinases CDK, EMT, FAK, Her1, Her2, IGF, IR, LCK, MET, PDGF, VEGF. The compds. I are also useful for the treatment of other diseases which can be treated by inhibiting tyrosine kinase enzymes.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:757186 CAPLUS

DOCUMENT NUMBER: 138:36791

TITLE: Epidermal growth factor receptor dependence in human tumors: more than just expression?

AUTHOR(S): Arteaga, Carlos L.

CORPORATE SOURCE: Departments of Medicine and Cancer Biology, and Vanderbilt-Ingram Comprehensive Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA

SOURCE: Oncologist (2002), 7(Suppl. 4), 31-39
CODEN: OCOLF6; ISSN: 1083-7159

PUBLISHER: AlphaMed Press

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The epidermal growth factor receptor (EGFR) is a rational target for antitumor strategies. EGFR signaling causes increased proliferation, decreased apoptosis, and enhanced tumor cell motility and neo-angiogenesis. The EGFR is expressed or highly expressed in a variety of human tumors of epithelial origin. ZD1839 (Iressa) is an orally active, selective EGFR tyrosine kinase inhibitor, which blocks signal transduction pathways implicated in proliferation and survival of cancer cells. The lack of a consistent method of evaluating levels of EGFR has caused a disparity in reports of the EGFR as a prognostic factor; however, for some tumors, EGFR is a strong prognostic indicator associated with more aggressive disease and reduced survival. So far, no clear association between EGFR levels and response to EGFR-targeted agents has been found. Preclin. studies with ZD1839 have noted a relationship between the two in some cases, but not others. EGFR signaling may be increased by a number of mechanisms in addition to high expression levels of EGFR, including receptor mutations, heterodimerization with other members of this receptor family such as HER2 (erbB2), increased expression of (autocrine/paracrine) ligands, and alterations in mols. that control receptor signaling output. Each of these components could be assessed to give an indication of the magnitude of EGFR signal amplification. Evaluation of signaling components downstream from EGFR should provide information on the activation of the EGFR pathway. Until EGFR-based assays predictive of a response to receptor-targeted therapies are available, there is no clear justification for stratifying patients by EGFR status or excluding patients with low EGFR levels from trials with ZD1839 or other EGFR inhibitors.

REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:601265 CAPLUS

DOCUMENT NUMBER: 138:147327

TITLE: Selective inhibition of the epidermal growth factor

receptor by ZD1839 decreases the growth and invasion of ovarian clear cell adenocarcinoma cells
AUTHOR(S): Fujimura, Masaki; Hidaka, Takao; Saito, Shigeru
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Faculty of Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan
SOURCE: Clinical Cancer Research (2002), 8(7), 2448-2454
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanism that regulates the growth of ovarian clear cell adenocarcinoma (CCA) are not well understood. The authors investigated the role of several growth factors that bind to membrane Tyr kinase receptors and added them to the ovarian CCA cell lines KK, RMG-1, and HAC-II to evaluate their effect on growth and cellular invasion. Epidermal growth factor and transforming growth factor-α significantly stimulated the growth and invasion of CCA cell lines in vitro. ZD1839, an epidermal growth factor receptor-tyrosine kinase inhibitor, decreased the growth and invasion of CCA cell lines in vitro and in vivo inhibited the growth of xenografts of the CCA cell line RMG-1. Severe combined immunodeficient mice bearing RMG-1 xenografts treated with ZD1839 survived for longer than the untreated control group. From these findings, the authors conclude that ZD1839 may offer a new and effective treatment for ovarian CCA.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:457389 CAPLUS
DOCUMENT NUMBER: 138:131509
TITLE: Selective Inhibition of the Epidermal Growth Factor Receptor Impairs Intestinal Adaptation after Small Bowel Resection
AUTHOR(S): O'Brien, David P.; Nelson, Lindsey A.; Williams, Jodi L.; Kemp, Christopher J.; Erwin, Christopher R.; Warner, Brad W.
CORPORATE SOURCE: Division of Pediatric Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45229, USA
SOURCE: Journal of Surgical Research (2002), 105(1), 25-30
CODEN: JSGRA2; ISSN: 0022-4804
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Prior indirect studies have suggested that a functional epidermal growth factor receptor (EGFR) appears to be indispensable for the adaptive response of the remnant intestine to massive small bowel resection (SBR). The recent availability of a specific pharmacol. EGFR inhibitor enabled us to more directly test the hypothesis that EGFR signaling is required for postresection intestinal adaptation. Methods: Mice (C57B1/6, n = 26) underwent a 50% SBR or sham operation and were then given orogastric EGFR inhibitor (ZD1839, 50 mg/kg/day) or vehicle. After 3 days, indexes of adaptation (wet weight, crypt depth, and villus height) and apoptotic index (number of apoptotic bodies per crypt) were calculated in the ileum. The expression of proliferating cell nuclear antigen (PCNA) and activated EGFR was measured by Western blotting. Results: ZD1839 prevented EGFR activation and the normal postresection increases in ileal wet weight, villus height, and crypt depth. Enterocyte proliferation was reduced twofold in the SBR group by ZD1839. Although not statistically significant, rates of enterocyte apoptosis were the highest in the inhibitor-treated mice. Conclusion: Following massive SBR, pharmacol. inhibition of the EGFR attenuates proliferation and the normal adaptive response of the intestine. These

results more directly confirm the requirement of a functional EGFR as a mediator of the postresection adaptation response. This study demonstrates an in vivo application of a novel selective EGFR inhibitor and offers a unique exptl. model to gain mechanistic insight into understanding postresection intestinal adaptation.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:408515 CAPLUS

DOCUMENT NUMBER: 136:395963

TITLE: Combination comprising an agent decreasing vascular endothelial growth factor (VEGF) activity and an agent decreasing epidermal growth factor (EGF) activity, and use in the treatment of diseases associated with deregulated angiogenesis

INVENTOR(S): Wood, Jeanette Marjorie; Brandt, Ralf; Bold, Guido; Traxler, Peter

PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH; Novartis Pharma GmbH

SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002041882	A2	20020530	WO 2001-EP13441	20011120 <--
WO 2002041882	A3	20020906		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ZM, ZW				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
CA 2427184	A1	20020530	CA 2001-2427184	20011120 <--
AU 200223684	A	20020603	AU 2002-23684	20011120 <--
EP 1339458	A2	20030903	EP 2001-997301	20011120
EP 1339458	B1	20070815		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004513964	T	20040513	JP 2002-544061	20011120
EP 1810715	A2	20070725	EP 2007-108093	20011120
R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE, TR, RO, SI				
US 2004034026	A1	20040219	US 2003-432303	20030521
US 2006270665	A1	20061130	US 2006-498027	20060802

PRIORITY APPLN. INFO.:		
GB 2000-28467	A	20001122
GB 2001-21813	A	20010910
EP 2001-997301	A3	20011120
WO 2001-EP13441	W	20011120
US 2003-432303	B1	20030521

OTHER SOURCE(S): MARPAT 136:395963

AB The invention discloses a combination comprising a first active ingredient which is a vasculostatic compound and a second active ingredient which decreases the activity of EGF, in particular for the delay of progression or treatment of a disease associated with deregulated angiogenesis, especially a proliferative disease. The invention also discloses a pharmaceutical composition comprising the combination; a com. package comprising the combination as a combined preparation; and a method of treatment of a warm-blooded animal, especially a human.

L6 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:71851 CAPLUS
DOCUMENT NUMBER: 136:112637
TITLE: Aromatase inhibitor-EGFR antagonist/inhibitor combined therapy for the treatment of hormone-dependent disorders and cancers
INVENTOR(S): Massimini, Giorgio; Piscitelli, Gabriella; Minardi, Giovanni
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002005791	A2	20020124	WO 2001-EP7676	20010704 <--
WO 2002005791	A3	20030103		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1315486	A2	20030604	EP 2001-978244	20010704
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004503582	T	20040205	JP 2002-511724	20010704
US 2005032759	A1	20050210	US 2003-333384	20030721
PRIORITY APPLN. INFO.:			GB 2000-17635 A	20000718
			WO 2001-EP7676 W	20010704

AB A method is provided for treating a human being suffering from a hormone-dependent disorder characterized by the overexpression of EGFR, comprising administering an aromatase inhibitor and an EGFR antagonist or EGFR inhibitor, in amts. effective to produce a superadditive or synergistic therapeutic effect.

L6 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:51035 CAPLUS
DOCUMENT NUMBER: 137:163394
TITLE: High levels of HER-2 expression alter the ability of epidermal growth factor receptor (EGFR) family tyrosine kinase inhibitors to inhibit EGFR phosphorylation in vivo
AUTHOR(S): Christensen, James G.; Schreck, Randall E.; Chan, Emily; Wang, Xueyan; Yang, Chris; Liu, Luna; Cui, Jean; Sun, Li; Wei, James; Cherrington, Julie M.; Mendel, Dirk B.
CORPORATE SOURCE: SUGEN, Inc., South San Francisco, CA, 94080, USA
SOURCE: Clinical Cancer Research (2001), 7(12), 4230-4238
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The epidermal growth factor receptor (EGFR) and HER-2 tyrosine kinases have been implicated in the development, progression, and severity of several human cancers and are attractive targets for therapeutic intervention. SU11925 was developed as a small mol. inhibitor of the

tyrosine kinase activity of both EGFR and HER-2. In cellular assays, SU11925 exhibited similar potency against EGFR and HER-2, inhibiting EGF-stimulated EGFR autophosphorylation in A431 (human epidermoid carcinoma) cells with an IC50 of 30 nM and HER-2 phosphorylation in SK-OV-3TP5 (human ovarian carcinoma) cells with an IC50 of 38 nM. In contrast to its similar activity against the two targets in cellular assays, .apprx.10-fold higher plasma concns. of SU11925 were required to inhibit HER-2 phosphorylation in HER-2-overexpressing tumors compared with EGFR phosphorylation in EGFR-overexpressing tumors in vivo. Consistent with the proposed mechanism of action of this inhibitor, SU11925 inhibited the s.c. growth of EGFR- and HER-2-dependent tumors in athymic mice at doses that produced substantial inhibition of target receptor phosphorylation in vivo. An unexpected finding from these studies was that higher plasma concns. of SU11925 were required to inhibit EGFR phosphorylation in vivo in tumors that also express high levels of HER-2 than in tumors that express EGFR alone. This observation, which suggests that it is more difficult to inhibit EGFR phosphorylation in vivo in cells that express high levels of HER-2, was confirmed with ZD1839 (Iressa), a selective EGFR inhibitor that also targets the tyrosine kinase catalytic site. The potential clin. implications of this observation are discussed.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:51027 CAPLUS

DOCUMENT NUMBER: 137:119184

TITLE: Oral administration of a novel taxane, an antisense oligonucleotide targeting protein kinase A, and the epidermal growth factor receptor inhibitor Iressa causes cooperative antitumor and antiangiogenic activity

AUTHOR(S): Tortora, Giampaolo; Caputo, Rosa; Damiano, Vincenzo; Fontanini, Gabriella; Melisi, Davide; Veneziani, Bianca Maria; Zunino, Franco; Bianco, A. Raffaele; Ciardiello, Fortunato

CORPORATE SOURCE: Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli Federico II, Naples, 80131, Italy

SOURCE: Clinical Cancer Research (2001), 7(12), 4156-4163
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purpose: Protein kinase A type I (PKAI) and the epidermal growth factor receptor (EGFR) play a role in neoplastic transformation and interact with each other in transducing mitogenic signals. The authors developed different PKAI and EGFR inhibitors, demonstrating their cooperation with cytotoxic drugs and the therapeutic potential of the combined blockade of PKAI and EGFR. In this study, the authors investigated the effect of orally active PKAI and EGFR inhibitors in combination with a novel taxane. Exptl. Design: the authors combined a hybrid PKAI antisense oligonucleotide sequence (AS-PKAI), the EGFR inhibitor ZD1839 (Iressa), and the taxane IDN5109, studying their effect on human cancer growth, apoptosis, and angiogenesis and measuring vascular endothelial growth factor (VEGF) expression and vessel formation in vitro and after oral administration in nude mice. Results: the authors demonstrated cooperative growth inhibitory and proapoptotic effects and inhibition of VEGF expression with any combination of two drugs and a marked synergistic effect when all three agents were combined. Oral administration of AS-PKAI, ZD1839, and IDN5109 in combination to nude mice caused a remarkable antitumor effect with no histol. evidence of tumors in 50% of mice 5 wk after treatment withdrawal, accompanied by complete suppression of vessel formation and

VEGF expression. Conclusion: This is the first demonstration of the cooperative antitumor and antiangiogenic activity of three novel agents that block multiple signaling pathways after oral administration. Because all agents are under clin. evaluation in cancer patients, the authors' results provide a rationale to translate this feasible therapeutic strategy in a clin. setting.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:799777 CAPLUS
DOCUMENT NUMBER: 137:27578
TITLE: A novel approach in the treatment of cancer: Targeting the epidermal growth factor receptor
AUTHOR(S): Ciardiello, Fortunato; Tortora, Giampaolo
CORPORATE SOURCE: Cattedra di Oncologia Medica. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli "Federico II,", Naples, 80131, Italy
SOURCE: Clinical Cancer Research (2001), 7(10), 2958-2970
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The critical role the EGFR plays in cancer has led to an extensive search for selective inhibitors of the EGFR signaling pathway. The results of a large body of preclin. studies and the early clin. trials thus far conducted suggest that targeting the EGFR could represent a significant contribution to cancer therapy. A variety of different approaches are currently being used to target the EGFR. The most promising strategies in clin. development include monoclonal antibodies to prevent ligand binding and small mol. inhibitors of the tyrosine kinase enzymic activity to inhibit autophosphorylation and downstream intracellular signaling. At least five blocking monoclonal antibodies have been developed against the EGFR. Among these, IMC-225 is a chimeric human-mouse monoclonal IgG1 antibody that has been the first anti-EGFR targeted therapy to enter clin. evaluation in cancer patients in Phase II and III studies, alone or in combination with conventional therapies, such as radiotherapy and chemotherapy. A number of small mol. inhibitors of the EGFR tyrosine kinase enzymic activity is also in development. OSI-774 and ZD1839 (Iressa) are currently in Phase II and III development, resp. ZD1839, a p.o. active, selective quinazoline derivative has demonstrated promising in vitro and in vivo antitumor activity. Preliminary results from Phase I and II trials in patients with advanced disease demonstrate that ZD1839 and OSI-774 have an acceptable tolerability profile and promising clin. efficacy in patients with a variety of tumor types. This mini-review describes the EGFR inhibitors in clin. development.

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:713163 CAPLUS
DOCUMENT NUMBER: 135:267215
TITLE: Combined treatment with keratinocyte growth factor and epidermal growth factor receptor (EGFR) inhibitor for reducing EGFR inhibitor-associated epithelial toxicity
INVENTOR(S): Miller, Penelope Elizabeth; Moyer, James Dale
PATENT ASSIGNEE(S): Pfizer Products, Inc., USA; OSI Pharmaceuticals, Inc.

SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070255	A2	20010927	WO 2001-US8207	20010315 <--
WO 2001070255	A3	20020228		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2403721	A1	20010927	CA 2001-2403721	20010315 <--
US 2002061304	A1	20020523	US 2001-808751	20010315 <--
EP 1276496	A2	20030122	EP 2001-916662	20010315
EP 1276496	B1	20050615		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003527437	T	20030916	JP 2001-568452	20010315
AT 297751	T	20050715	AT 2001-916662	20010315
ES 2240430	T3	20051016	ES 2001-1916662	20010315
MX 2002PA09176	A	20040812	MX 2002-PA9176	20020919
US 2004071697	A1	20040415	US 2003-458072	20030610
PRIORITY APPLN. INFO.:			US 2000-190697P	P 20000320
			US 2001-808751	B1 20010315
			WO 2001-US8207	W 20010315

AB Compns. and methods are provided for treating the epithelial toxicity caused by administering to a human cancer patient an epidermal growth factor receptor (EGFR) inhibitor. The pharmaceutical composition preferably comprises an EGFR inhibitor and a keratinocyte growth factor (KGF) in a pharmaceutically acceptable carrier. The method of treatment comprises co-administering to the patient a therapeutically effective amount of KGF with the EGFR inhibitor.

=> D his

(FILE 'HOME' ENTERED AT 11:26:28 ON 06 SEP 2007)

FILE 'REGISTRY' ENTERED AT 11:26:43 ON 06 SEP 2007
L1 1 S ZD 1839/CN

FILE 'CAPLUS' ENTERED AT 11:27:28 ON 06 SEP 2007
L2 1458 S L1
L3 2839 S ZENECA/CS
L4 1458 S L1 AND L2
L5 182 S L1 AND (EGF INHIBITOR OR EGFR INHIBITOR)
L6 11 S L5 AND PY<2003

=> S L2 and L3
L7 6 L2 AND L3

=> D L7 1-6 ibib abs

L7 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:360558 CAPLUS

DOCUMENT NUMBER: 137:362240
TITLE: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, ZD1839 profile
AUTHOR(S): Kamano, Seimin; Yano, Seiichi; Dong, Rui-Ping
CORPORATE SOURCE: Clinical Strategy Department, Research & Development, Astra Zeneca K. K., Kita-ku, Osaka-shi, Osaka, 531-0076, Japan
SOURCE: Saibo (2002), 34(4), 170-173
CODEN: SAIBC7; ISSN: 1346-7557
PUBLISHER: Nyu Saiensusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, discussing the action mechanism, clin. pharmacol. and toxicity of ZD1839 as an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor and angiogenesis inhibitor for treatment of cancer.

L7 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:539320 CAPLUS
DOCUMENT NUMBER: 136:79038
TITLE: EGFR tyrosine kinase inhibitors in the treatment of cancer
AUTHOR(S): Barker, Andrew J.
CORPORATE SOURCE: Zeneca Pharmaceuticals, Macclesfield, SK10 4TG, UK
SOURCE: Special Publication - Royal Society of Chemistry (2001), 264(Medicinal Chemistry into the Millennium), 140-147
CODEN: SROCDO; ISSN: 0260-6291
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, discussing the signaling system acting through the epidermal growth factor (EGF) receptor tyrosine (RT) kinase, which is of particular interest as it was over-expressed in a high proportion of human solid tumors and its expression was related to poor patient prognosis. It also discusses ZD 1839, which is identified as a highly potent compound against EGF RT kinase and while it had activity against other class I RTK, it did not inhibit a variety of other kinases indicating good selectivity.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:50631 CAPLUS
DOCUMENT NUMBER: 134:100885
TITLE: Preparation of quinazolinyl ureas, thioureas and guanidines for use in the prevention or treatment of T cell mediated diseases or medical conditions
INVENTOR(S): Crawley, Graham Charles; McKerrecher, Darren; Poyser, Jeffrey Philip; Hennequin, Laurent Francois Andre; Ple, Patrick; Lambert, Christine Marie-Paul
PATENT ASSIGNEE(S): Astrazeneca UK Limited, UK; Zeneca Pharma S.A.
SOURCE: PCT Int. Appl., 169 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

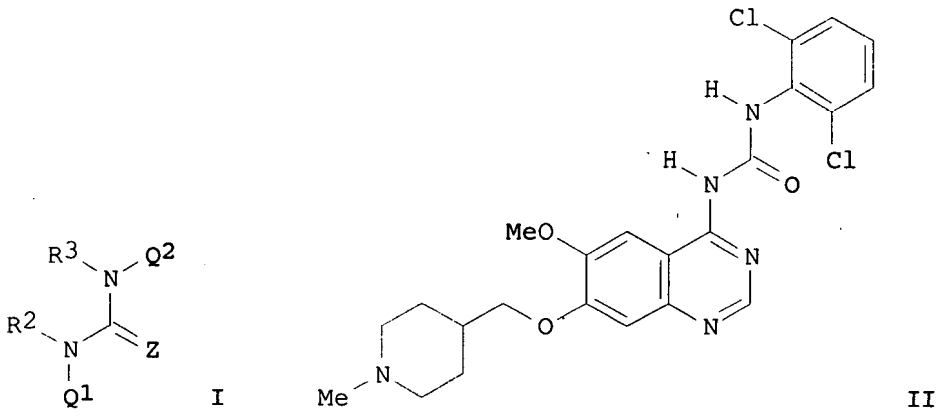
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001004102	A1	20010118	WO 2000-GB2566	20000704

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,

LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2378291	A1	20010118	CA 2000-2378291		20000704
BR 2000012157	A	20020402	BR 2000-12157		20000704
EP 1218353	A1	20020703	EP 2000-953271		20000704
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
JP 2003504360	T	20030204	JP 2001-509712		20000704
ZA 2001009864	A	20030228	ZA 2001-9864		20011129
MX 2001PA12887	A	20020730	MX 2001-PA12887		20011213
NO 2002000042	A	20020304	NO 2002-42		20020104
US 6806274	B1	20041019	US 2002-19945		20020107
PRIORITY APPLN. INFO.:			EP 1999-401692	A	19990707
			EP 2000-401221	A	20000504
			WO 2000-GB2566	W	20000704

OTHER SOURCE(S): MARPAT 134:100885
GI



AB The title compds. [I; Q1 = quinazoline ring optionally substituted with halo, CF3 or CN, or a group X1Q3 (wherein X1 = a direct bond, O; Q3 = aryl, arylalkyl, heterocyclyl, (heterocyclyl)alkyl); R2, R3 = H, alkyl; Z = O, S, NH; Q2 = aryl, arylalkyl] and their pharmaceutically-acceptable salts, useful in the prevention or treatment of T cell mediated diseases or medical conditions such as transplant rejection or rheumatoid arthritis, were prepared and formulated. E.g., a multi-step synthesis of the urea II was given. In general, activity possessed by compds. I may be demonstrated at IC50 of 0.0001- 5 μM against enzyme p56lck binding and IC50 of 0.001-10 μM in in vitro T cell proliferation assay (T cell receptor stimulation).

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:166618 CAPLUS
DOCUMENT NUMBER: 130:209715
TITLE: Preparation of oxindolylquinazolines as angiogenesis inhibitors
INVENTOR(S): Hennequin, Laurent Francois Andre; Ple, Patrick; Lohmann, Jean-Jacques Marcel; Thomas, Andrew Peter
PATENT ASSIGNEE(S): Zeneca Limited, UK; Zeneca-Pharma S.A.
SOURCE: PCT Int. Appl., 135 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9910349	A1	19990304	WO 1998-GB2493	19980819
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9888162	A	19990316	AU 1998-88162	19980819
EP 1005470	A1	20000607	EP 1998-939756	19980819
EP 1005470	B1	20070801		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2001514182	T	20010911	JP 2000-507677	19980819
US 6294532	B1	20010925	US 2000-486051	20000503

PRIORITY APPLN. INFO.:

EP 1997-401972	A	19970822
EP 1997-401973	A	19970822
EP 1997-401974	A	19970822
WO 1998-GB2493	W	19980819

OTHER SOURCE(S): MARPAT 130:209715
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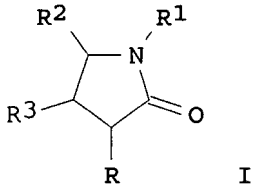

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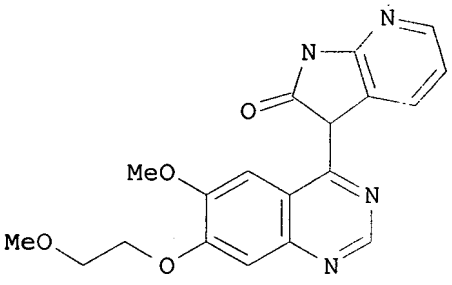


II

AB Title compds. [I; R = 5-8 (un)substituted 4-quinazolinyl; R1 = H, alkyl, (di)alkoxymethyl, alkanoyl; R2R3 = atoms to complete a heterocyclic ring] were prepared as angiogenesis inhibitors (no data). Thus, 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline (preparation given) was condensed with 7-azaoxindole to give title compound II.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

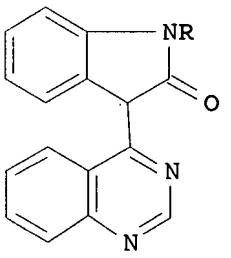
L7 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:756964 CAPLUS
DOCUMENT NUMBER: 128:22920
TITLE: Oxindolylquinazoline derivatives as angiogenesis inhibitors
INVENTOR(S): Thomas, Andrew Peter; Hennequin, Laurent Francois Andre; Lohmann, Jean-jacques Marcel; Ple, Patrick
PATENT ASSIGNEE(S): Zeneca Limited, UK; Zeneca Pharma S.A.; Thomas, Andrew Peter; Hennequin, Laurent Francois Andre; Lohmann, Jean-Jacques Marcel; Ple, Patrick
SOURCE: PCT Int. Appl., 164 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9742187	A1	19971113	WO 1997-GB1211	19970502
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9726475	A	19971126	AU 1997-26475	19970502
EP 912557	A1	19990506	EP 1997-918293	19970502
EP 912557	B1	20030709		
R: CH, DE, FR, GB, IT, LI				
JP 2000510115	T	20000808	JP 1997-539644	19970502
ZA 9703844	A	19971106	ZA 1997-3844	19970505
IN 1997DE01160	A	20050311	IN 1997-DE1160	19970505
US 6265411	B1	20010724	US 1998-180310	19981106

PRIORITY APPLN. INFO.:	EP 1996-400956	A	19960506
	EP 1996-400957	A	19960506
	EP 1996-402762	A	19961217
	EP 1996-402763	A	19961217
	WO 1997-GB1211	W	19970502

OTHER SOURCE(S): MARPAT 128:22920
GI



I

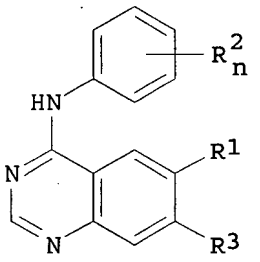
AB Title compds. I [R = H, alkyl, alkoxymethyl, dialkoxymethyl, alkanoyl and the benzene rings may be further substituted] were prepared for use in inhibiting angiogenesis and reducing vascular permeability (no data). Thus, 4,5-dimethoxyanthranilic acid was converted to 6,7-dimethoxyquinazoline by treatment with HCONH2 and was treated with 1-methyloxindole to give 6,7-dimethoxy-4-(1-methyl-3-oxindolyl)quinazoline.

L7 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:756469 CAPLUS
DOCUMENT NUMBER: 126:47235
TITLE: Preparation of haloanilinoquinazolines as Class I receptor tyrosine kinase inhibitors
INVENTOR(S): Gibson, Keith Hopkinson
PATENT ASSIGNEE(S): Zeneca Limited, UK
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9633980	A1	19961031	WO 1996-GB961		19960423
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI					
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN					
TW 436486	B	20010528	TW 1996-85104049		19960408
IN 1996DE00841	A	20050311	IN 1996-DE841		19960419
CA 2215732	A1	19961031	CA 1996-2215732		19960423
CA 2215732	C	20020409			
AU 9653433	A	19961118	AU 1996-53433		19960423
AU 699163	B2	19981126			
EP 823900	A1	19980218	EP 1996-910134		19960423
EP 823900	B1	20001227			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI					
CN 1182421	A	19980520	CN 1996-193526		19960423
CN 1100046	B	20030129			
BR 9608082	A	19990126	BR 1996-8082		19960423
HU 9802839	A2	19990329	HU 1998-2839		19960423
HU 223313	B1	20040528			
JP 11504033	T	19990406	JP 1996-532252		19960423
JP 3040486	B2	20000515			
RU 2153495	C2	20000727	RU 1997-119521		19960423
AT 198329	T	20010115	AT 1996-910134		19960423
ES 2153098	T3	20010216	ES 1996-910134		19960423
PT 823900	T	20010430	PT 1996-910134		19960423
CZ 288489	B6	20010613	CZ 1997-3396		19960423
EE 3482	B1	20010815	EE 1997-252		19960423
SK 282236	B6	20011203	SK 1997-1454		19960423
RO 117849	B1	20020830	RO 1997-1978		19960423
PL 189182	B1	20050729	PL 1996-323066		19960423
HR 960204	B1	20011031	HR 1996-204		19960425
ZA 9603358	A	19961028	ZA 1996-3358		19960426
US 5770599	A	19980623	US 1996-638331		19960426
IL 118045	A	20011031	IL 1996-118045		19960426
NO 9704940	A	19971024	NO 1997-4940		19971024
NO 309472	B1	20010205			
HK 1005371	A1	20011116	HK 1998-104504		19980525
GR 3035211	T3	20010430	GR 2001-400025		20010111
IN 2003DE01419	A	20051125	IN 2003-DE1419		20031117
IN 2003DE01420	A	20051125	IN 2003-DE1420		20031117
PRIORITY APPLN. INFO.:			GB 1995-8538	A	19950427
			IN 1996-DE841	A3	19960419
			WO 1996-GB961	W	19960423
			IN 2003-DE908	A3	20030718

OTHER SOURCE(S): MARPAT 126:47235
GI



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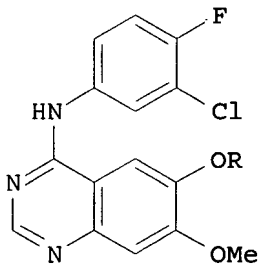

II

AB Title compds. (I; R1 = dialkylaminoalkoxy, pyrrolidinoalkoxy, piperidinoalkoxy, etc.; R2 = halo, CF3, alkyl; R3 = alkoxy; n = 1-3) were prepared Thus, 6,7-dimethoxy-3,4-dihydroquinazolin-4-one was converted in 3 steps to 6-acetoxy-4-chloro-7-methoxyquinazoline which was aminated by 4,3-FClC6H3NH2 and the product saponified to give title compound II (R = H). The latter was etherified by 3-morpholinopropyl chloride to give II (R = 3-morpholinopropyl). Data for biol. activity of I were given.

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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	68.63	76.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
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